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(21) International Application Number: PCT/US99/30735 (22) International Filing Date: 21 December 1999 (21.12.99) (30) Priority Data: 60/113,627 23 December 1998 (23.12.98) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]: Chestnut Run Plaza, 974 Centre Road, Wilmington, DE 19807 (US). (72) Inventors: WEXLER, Ruth, R.; 2205 Patwynn Road, Wilmington, DE 19810 (US). CLARK, Charles, G.; 4 Glenview Place, Cherry Hill, NJ 08034 (US). FEVIG, John, M.; 987 Church Road, Lincoln University, PA 19352 (US). GALEMMO, Robert, A.; 3039 Stump Hill Road, Collegeville, PA 19426 (US). HAN, Qi; 2609 Marhill Road, Wilmington, DE 19810 (US). JACOBSON, Irina, C.; 3205 Heathwood Road, Wilmington, DE 19810 (US). LAM, Patrick, Yuk, Sun; 6 Ridgeway Drive, Chadds Ford, PA 19317 (US). LI, Hui, Yin; 161 Thompson Road, Hockessin, DE 19707 (US). PINTO, Donald, J., P.; 39 Whitson Drive, Newark, DE 19702 (US).		(74) Agent: VANCE, David, H.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US). (81) Designated States: AL, AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: THROMBIN OR FACTOR Xa INHIBITORS		
(57) Abstract		
This invention relates generally to inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.		

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TITLE

Thrombin or Factor Xa Inhibitors

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FIELD OF THE INVENTION

This invention relates generally to inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

10

BACKGROUND OF THE INVENTION

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: *Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. Thromb. Res.* 1979, 15, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

20

Therefore, efficacious and specific inhibitors of factor Xa, thrombin, or both are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa, thrombin, or both inhibitors.

30

35

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel nitrogen containing aromatic heterocycles,

with ortho-substituted P1 groups, which are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

5 It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

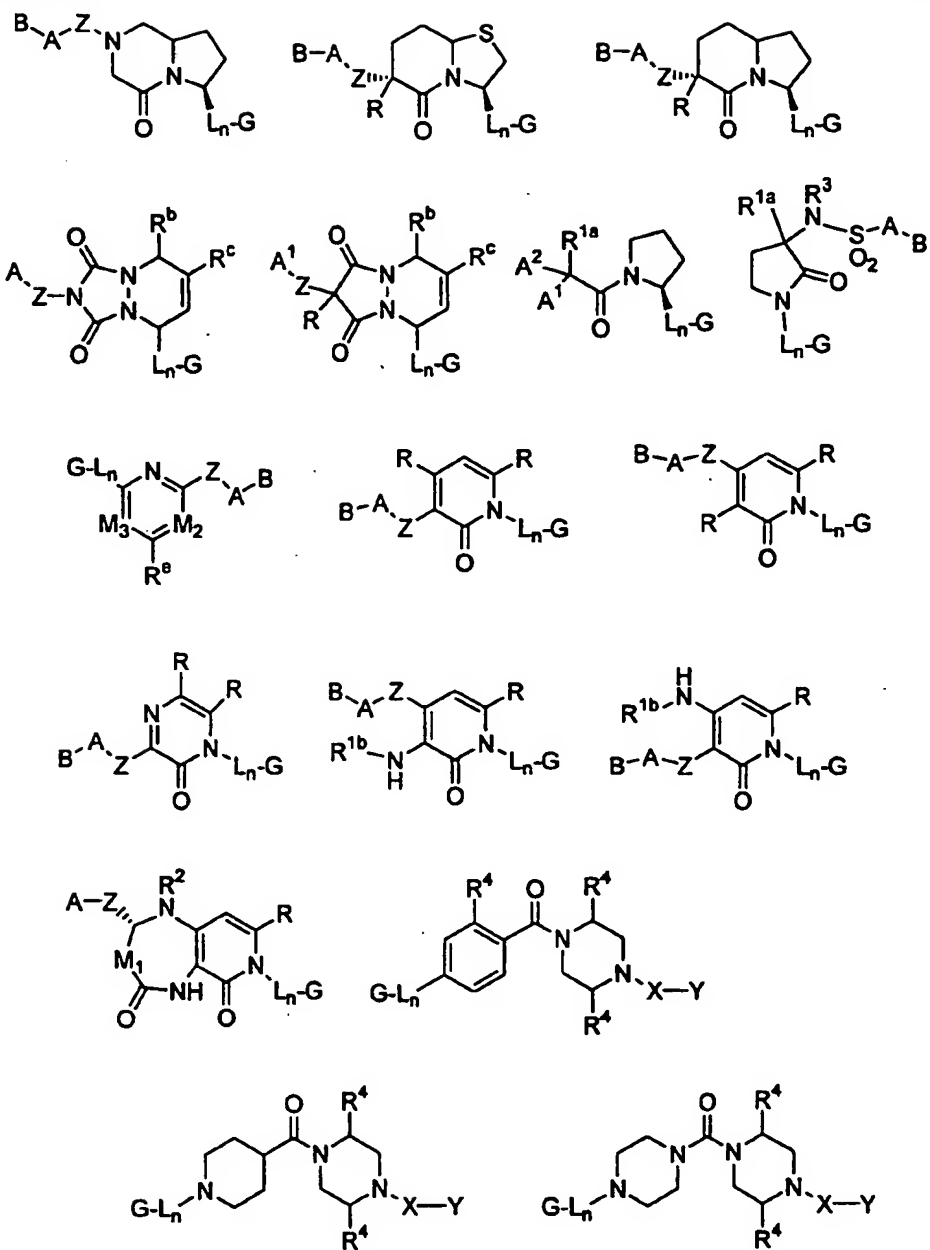
10 It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

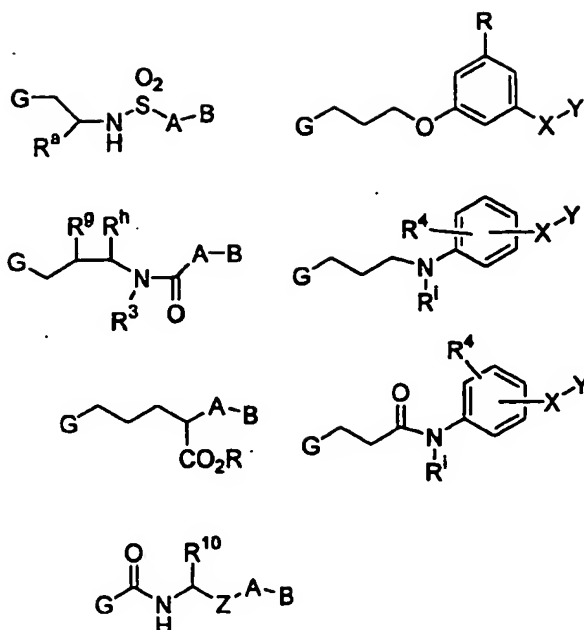
15 It is another object of the present invention to provide novel compounds for use in therapy.

20 It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of thrombosis or a disease mediated by factor Xa.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides
25 a novel compound selected from the group:

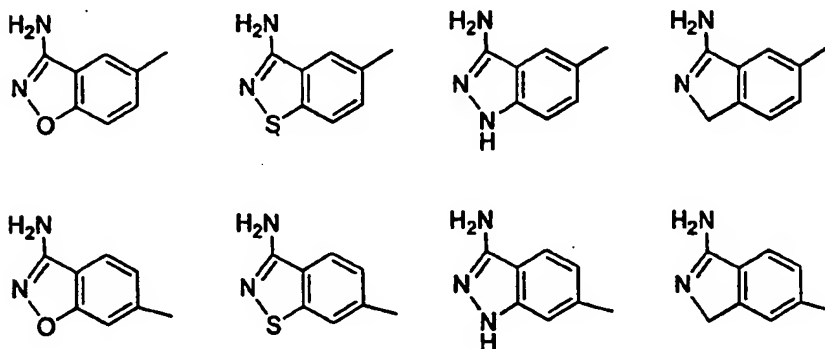


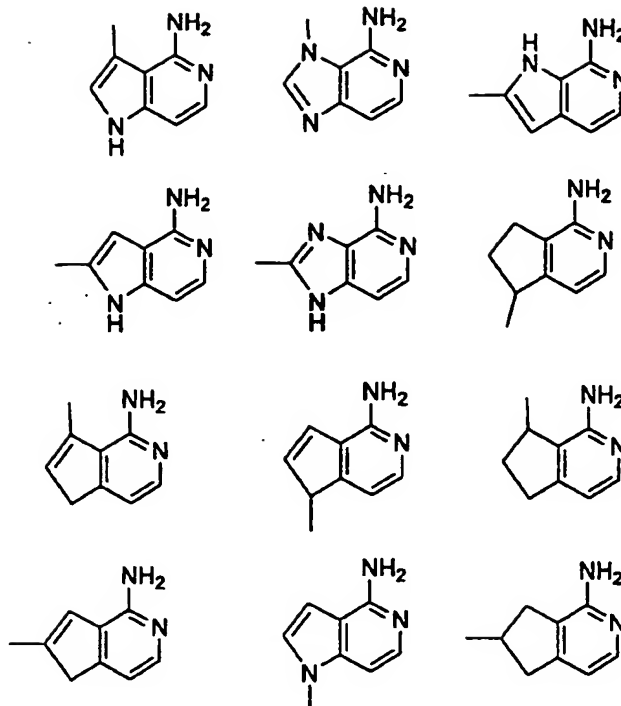


or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

5

G is selected from the group:





L_n is a linker which is absent or is selected from O, S, CH_2 ,

$*CH_2NHC(O)$, $*CH(R^a)NHC(O)$, $*CH_2NHC(O)CH_2$, and

5 $*CH(R^a)NHC(O)CH_2$, provided that L_n and M do not form an O-N or S-N bond and the * indicates where L_n is bonded to G;

M^1 is absent or is CHR;

10

M^2 is N or CR^f ;

M^3 is N or CR^d ;

15 provided that only one of M^2 and M^3 is N;

R^a is selected from $C(O)C(O)OR^3$, $C(O)C(O)NR^2R^{2a}$, and $C(O)-A$;

R^b is selected from H, R, phenyl, C_{1-10} alkyl, and C_{2-5}
20 alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

5

R^d is selected from H, F, and Cl;

R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

10

15

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1b}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

R^f is selected from H, F, and Cl;

20

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1b}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

R^g is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

25

R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

R^i is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and $C(O)OR^3$;

30

R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, benzyl, OCF_3 , CF_3 , $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

Z is selected from a $(CR^8R^9)_{1-4}$, $(CR^8R^9)_rO(CR^8R^9)_r$, $(CR^8R^9)_rNR^3(CR^8R^9)_r$, $(CR^8R^9)_rC(O)(CR^8R^9)_r$,

- $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O}) (\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O}) (\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{OC}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$,
5 $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_p(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_2(\text{CH}=\text{CH})$,
 $(\text{CCR}^8\text{R}^9)_r\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2(\text{CR}^8\text{R}^9)_r$, and
 $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, provided that Z does not form
a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with the
groups to which Z is attached;

10

R^{1a} is absent or selected from $-(\text{CH}_2)_r\text{-R}^{1'}$, $-\text{CH}=\text{CH-R}^{1'}$,
 $\text{NHCH}_2\text{R}^{1''}$, $\text{OCH}_2\text{R}^{1''}$, $\text{SCH}_2\text{R}^{1''}$, $\text{NH}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$,
 $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$;

- 15 $\text{R}^{1'}$ is selected from H, C₁₋₃ alkyl, F, Cl, Br, I, -CN, -CHO,
 $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OR}^2$, NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $\text{OC}(\text{O})\text{R}^2$,
 $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$, $\text{S}(\text{O})_p(\text{CH}_2)_r\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$,
 $\text{C}(=\text{NR}^{2c})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$,
 $\text{OC}(\text{O})\text{NR}^{2a}\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$,
20 $\text{NR}^2\text{SO}_2\text{R}^{2b}$, C₃₋₆ carbocyclic residue substituted with 0-2
 R^4 , and 5-10 membered heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R^4 ;

- 25 $\text{R}^{1''}$ is selected from H, $\text{CH}(\text{CH}_2\text{OR}^2)_2$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
 $\text{S}(\text{O})\text{R}^{2b}$, $\text{S}(\text{O})_2\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted
with A;

30

R^2 , at each occurrence, is selected from H, CF_3 , C₁₋₆ alkyl,
benzyl, C₃₋₆ carbocyclic residue substituted with 0-2

R^{4b} , and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;

5 R^{2a} , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} cycloalkylmethyl substituted with 0-2 R^{4b} , C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O,
10 and S substituted with 0-2 R^{4b} ;

R^{2b} , at each occurrence, is selected from CF_3 , C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system
15 containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;

R^{2c} , at each occurrence, is selected from CF_3 , OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic
20 system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;

25 alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group
30 consisting of N, O, and S;

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

5 R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and phenyl;

10 A is selected from:

C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

15

A¹ is H or A;

alternatively, A and A¹ and the carbon to which they are attached combine to form fluorene;

20

A² is selected from H, A, and CHA³A⁴;

A³ is selected from H, A, C₁₋₄ alkyl, and -(CH₂)_tNR²R^{2a};

25 A⁴ is H or A;

B is selected from: H, Y, and X-Y

30 X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -CR²(NR^{1''}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O), -OS(O)₂-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, 35 -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-,

-NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and
-OCR²R^{2a}-;

Y is selected from:

5 (CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N,
or S-N bond,

C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and

5-10 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O, and
10 S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
15 Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a},
C(=NR²)NR²R^{2a}, C(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a},
C(O)NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄
alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, NHCH₂R^{1''}, OCH₂R^{1''},
20 SCH₂R^{1''}, N(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and
S(CH₂)₂(CH₂)_tR^{1'};

alternatively, one R⁴ is a 5-6 membered aromatic heterocycle
containing from 1-4 heteroatoms selected from the group
25 consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
(CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, Cl, Br, F, I, C₁₋₄ alkyl,
-CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b},
30 C(O)NR²R^{2a}, C(O)NH(CH₂)₂NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)R^{3c},
C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a},
NR²SO₂-C₁₋₄ alkyl, C(O)NHSO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
S(O)_pR⁵, and (CF₂)_rCF₃;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R^5 ;

5

R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;

10

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl substituted with 0-2 R^6 , and benzyl substituted with 0-2 R^6 ;

15

R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

20

R^7 , at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, $(CH_2)_n$ -phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

25

R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$ -phenyl;

30

alternatively, R⁷ and R⁸ combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

5

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;

10

R¹⁰ is selected from H, phenyl substituted with 0-2 R^{4a}, and naphthyl substituted with 0-2 R^{4a};

n, at each occurrence, is selected from 0, 1, 2, and 3;

15

m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

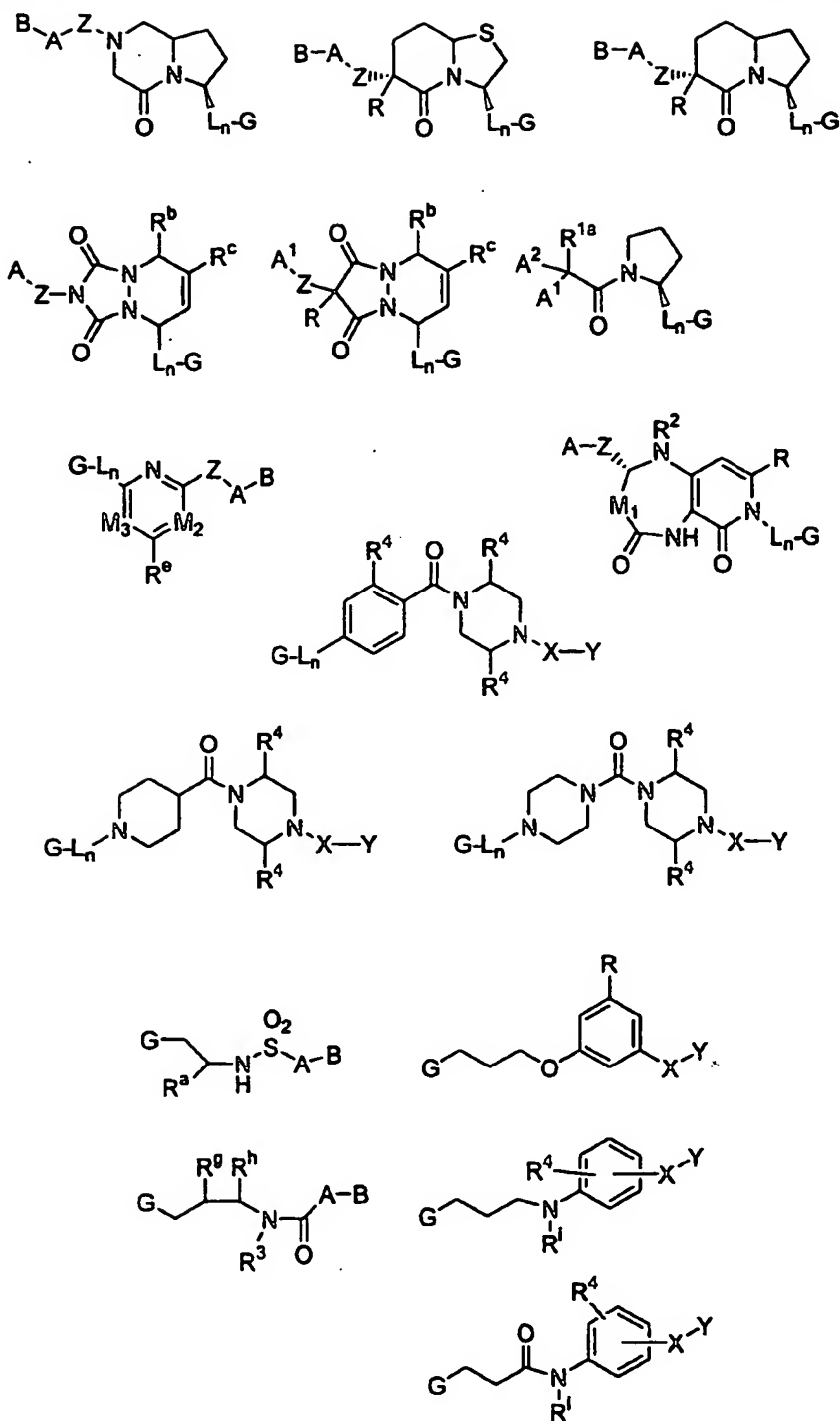
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s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

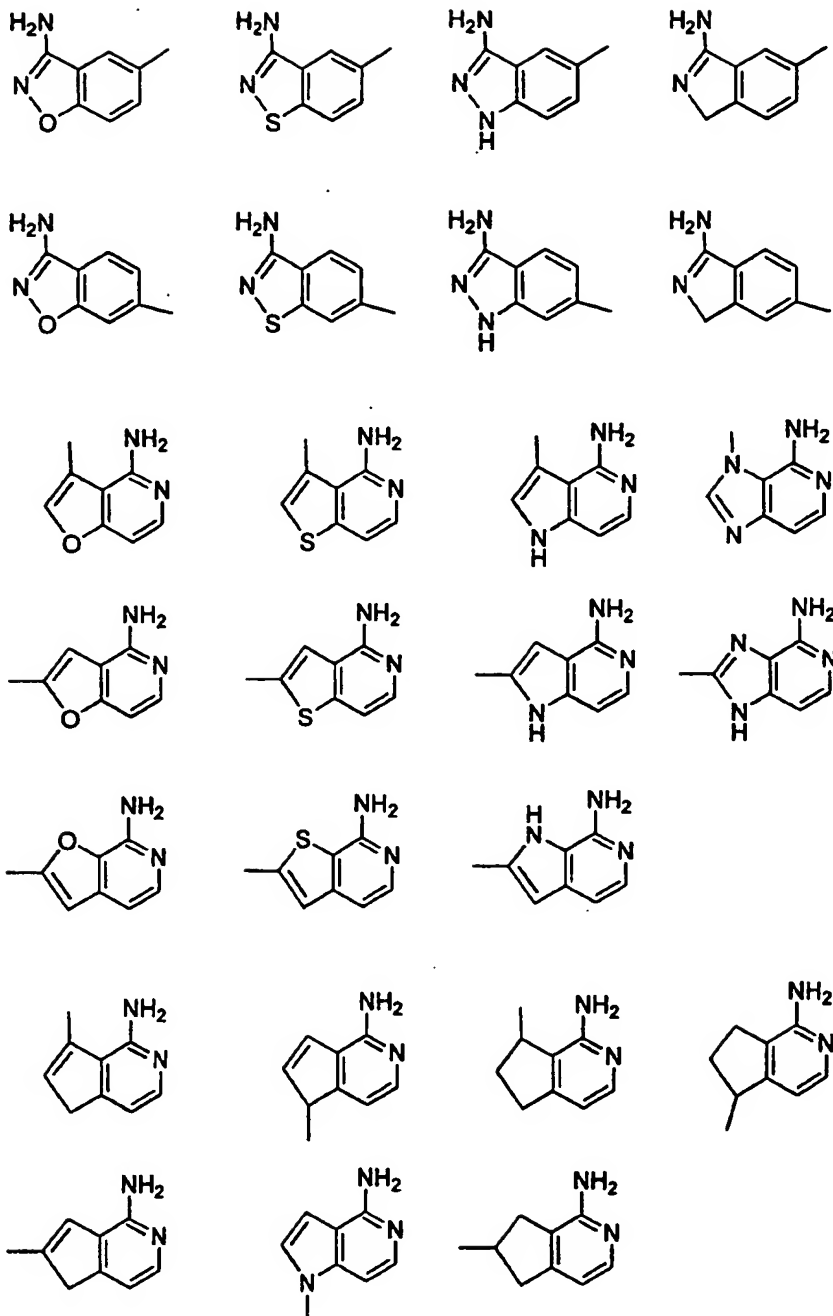
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[2] Thus, in another embodiment, the present invention provides a novel compound selected from the group:



5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from the group:



5

10

L_n is a linker which is absent or is selected from O, S, CH₂,
 *CH₂NHC(O), *CH(R^a)NHC(O), *CH₂NHC(O)CH₂, and
 *CH(R^a)NHC(O)CH₂, provided that L_n and M do not form an

O-N or S-N bond and the * indicates where L_n is bonded to G;

M^1 is absent or is CHR;

5

M^2 is N or CR^f ;

M^3 is N or CR^d ;

10 provided that only one of M^2 and M^3 is N;

R^a is selected from $C(O)C(O)OR^3$, $C(O)C(O)NR^2R^{2a}$, and $C(O)-A$;

15 R^b is selected from H, R, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

20 alternatively, R^b and R^c together are $-(CH_2)_4-$;

R^d is selected from H, F, and Cl;

25 R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

30 alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1b}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

R^f is selected from H, F, and Cl;

35 alternatively, R^e and R^f combine to form $-NR^3-C(R^{1b}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

R^9 is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

5 R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

R^i is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and $C(O)OR^3$;

10 R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, benzyl, OCF_3 , CF_3 , $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

Z is selected from a $(CR^8R^9)_{1-4}$, $(CR^8R^9)_rO(CR^8R^9)_r$,
 $(CR^8R^9)_rNR^3(CR^8R^9)_r$, $(CR^8R^9)_rC(O)(CR^8R^9)_r$,
 15 $(CR^8R^9)_rC(O)O(CR^8R^9)_r$, $(CR^8R^9)_rOC(O)(CR^8R^9)_r$,
 $(CR^8R^9)_rC(O)NR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3C(O)(CR^8R^9)_r$,
 $(CR^8R^9)_rOC(O)O(CR^8R^9)_r$, $(CH_2)_rOC(O)NR^3(CR^8R^9)_r$,
 $(CR^8R^9)_rNR^3C(O)O(CR^8R^9)_r$, $(CH_2)_rNR^3C(O)NR^3(CR^8R^9)_r$,
 $(CR^8R^9)_rS(O)_p(CR^8R^9)_r$, $(CR^8R^9)_rS(O)_2(CH=CH)$,
 20 $(CCR^8R^9)_rSO_2NR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3SO_2(CR^8R^9)_r$, and
 $(CR^8R^9)_rNR^3SO_2NR^3(CR^8R^9)_r$, provided that Z does not form
 a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with the
 groups to which Z is attached;

25 R^{1a} is absent or selected from $-(CH_2)_r-R^{1'}$, $-CH=CH-R^{1'}$,
 $NHCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $NH(CH_2)_2(CH_2)_tR^{1'}$,
 $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

$R^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, $-CN$, $-CHO$,
 30 $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a} , $C(O)R^{2c}$, $OC(O)R^2$,
 $(CF_2)_rCO_2R^{2c}$, $S(O)_p(CH_2)_rR^{2b}$, $NR^2(CH_2)_rOR^2$,

C(=NR^{2c})NR²R^{2a}, NR²C(O)R^{2b}, NR²C(O)NHR^{2b}, NR²C(O)₂R^{2a},
OC(O)NR^{2a}R^{2b}, C(O)NR²R^{2a}, C(O)NR²(CH₂)_xOR², SO₂NR²R^{2a},
NR²SO₂R^{2b}, C₃₋₆ carbocyclic residue substituted with 0-2
R⁴, and 5-10 membered heterocyclic system containing
5 from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R⁴;

R^{1''} is selected from H, CH(CH₂OR²)₂, C(O)R^{2c}, C(O)NR²R^{2a},
S(O)R^{2b}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

10

R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted
with A;

R², at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl,
15 benzyl, C₃₋₆ carbocyclic residue substituted with 0-2
R^{4b}, and 5-6 membered heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R^{4b};

20 R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl,
benzyl, C₃₋₆ cycloalkylmethyl substituted with 0-2 R^{4b},
C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and
5-6 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O,
25 and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy,
C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted
with 0-2 R^{4b}, and 5-6 membered heterocyclic system
30 containing from 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and phenyl;

A is selected from:
C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

A¹ is H or A;

alternatively, A and A¹ and the carbon to which they are attached combine to form fluorene;

A² is selected from H, A, and CHA³A⁴;

5

A³ is selected from H, A, C₁₋₄ alkyl, and -(CH₂)_rNR²R^{2a};

A⁴ is H or A;

10 B is selected from: H, Y, and X-Y

X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -CR²(NR¹'R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -OS(O)₂-, -S(O)_p-, -S(O)_pCR²R^{2a}-,
 15 -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and
 20 -OCR²R^{2a}-;

Y is selected from:

(CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,

25 C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

30 alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a},

$C(=NR^2)NR^2R^{2a}$, $C(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$,
 $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$
 alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $NHCH_2R^{1''}$, $OCH_2R^{1''}$,
 $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and
 5 $S(CH_2)_2(CH_2)_tR^{1'}$;

alternatively, one R^4 is a 5-6 membered aromatic heterocycle
 containing from 1-4 heteroatoms selected from the group
 consisting of N, O, and S;

10

R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$,
 $(CH_2)_r-F$, $(CH_2)_r-Br$, $(CH_2)_r-Cl$, Cl, Br, F, I, C_{1-4} alkyl,
 -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$,
 $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)R^{3c}$,
 15 $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$,
 $NR^2SO_2-C_{1-4}$ alkyl, $C(O)NHSO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$,
 $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle
 20 containing from 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-1 R^5 ;

R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$,
 F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$,
 25 $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$,
 $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$,
 $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl,
 $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;

30 R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl,
 phenyl substituted with 0-2 R^6 , and benzyl substituted
 with 0-2 R^6 ;

- R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;
- R^7 , at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxy carbonyl, $(CH_2)_n$ -phenyl, C_{6-10} aryloxy, C_{6-10} aryloxy carbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxy carbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxy carbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxy carbonyl;
- R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$ -phenyl;
- alternatively, R^7 and R^8 combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;
- R^9 , at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$ -phenyl;
- R^{10} is selected from H, phenyl substituted with 0-2 R^{4a} , and naphthyl substituted with 0-2 R^{4a} ;
- n , at each occurrence, is selected from 0, 1, 2, and 3;
- m , at each occurrence, is selected from 0, 1, and 2;
- p , at each occurrence, is selected from 0, 1, and 2;

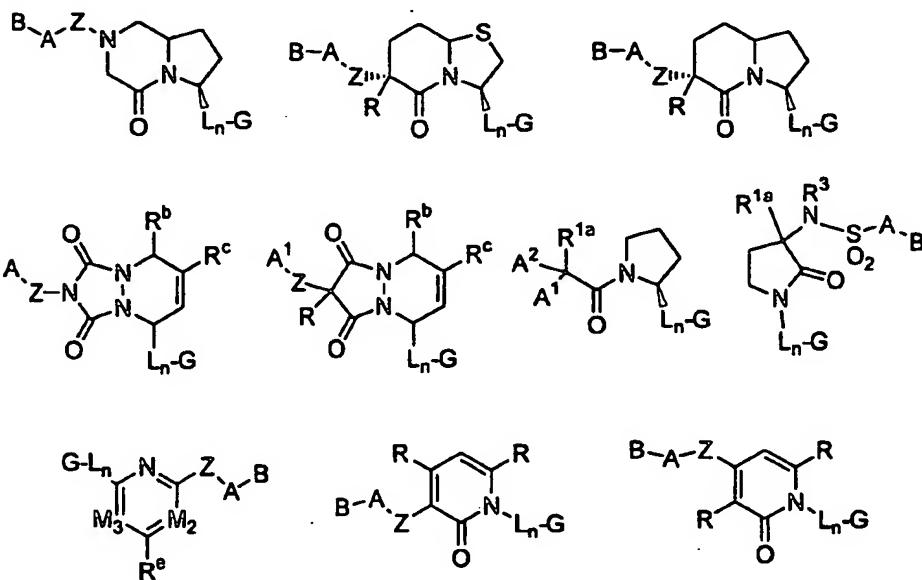
r, at each occurrence, is selected from 0, 1, 2, and 3;

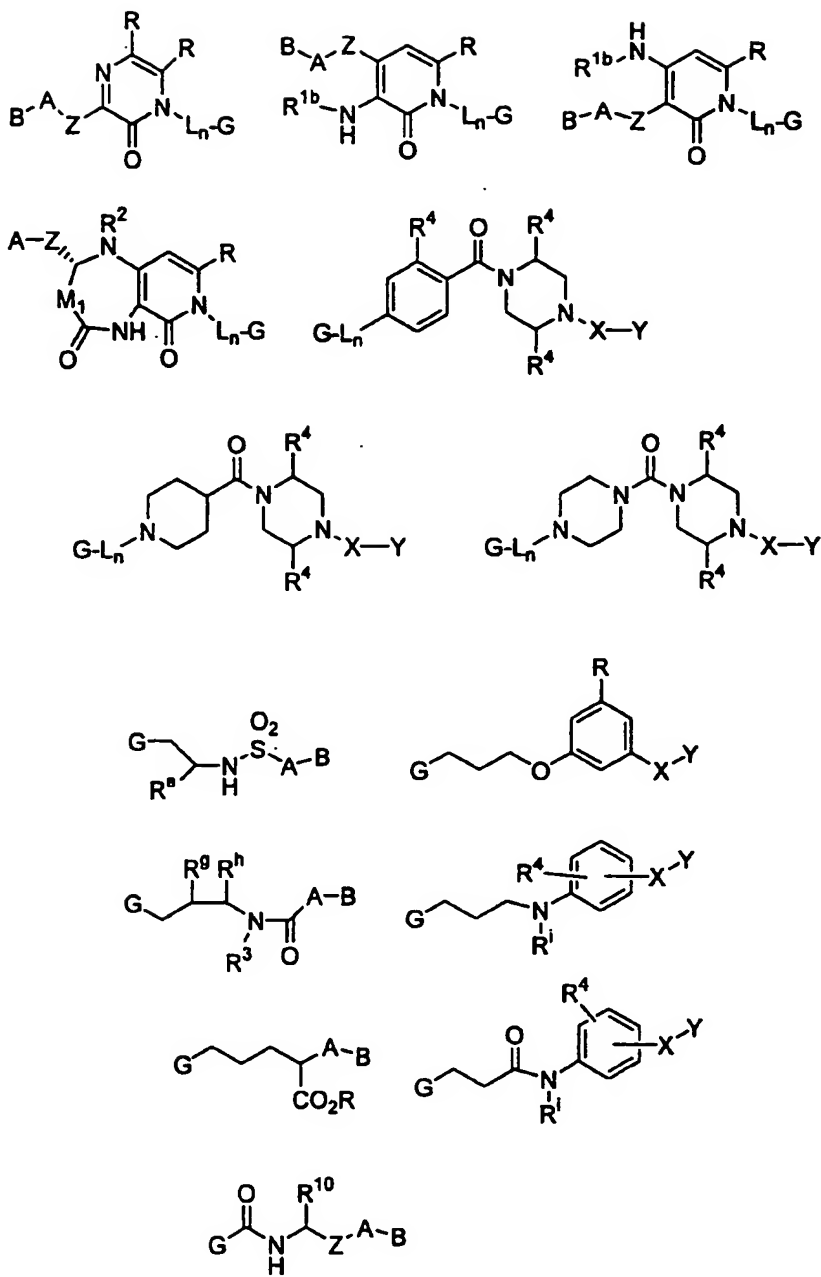
s, at each occurrence, is selected from 0, 1, and 2; and,

5 t, at each occurrence, is selected from 0, 1, 2, and 3.

[3] Thus, in another embodiment, the present invention provides a novel compound selected from the group:

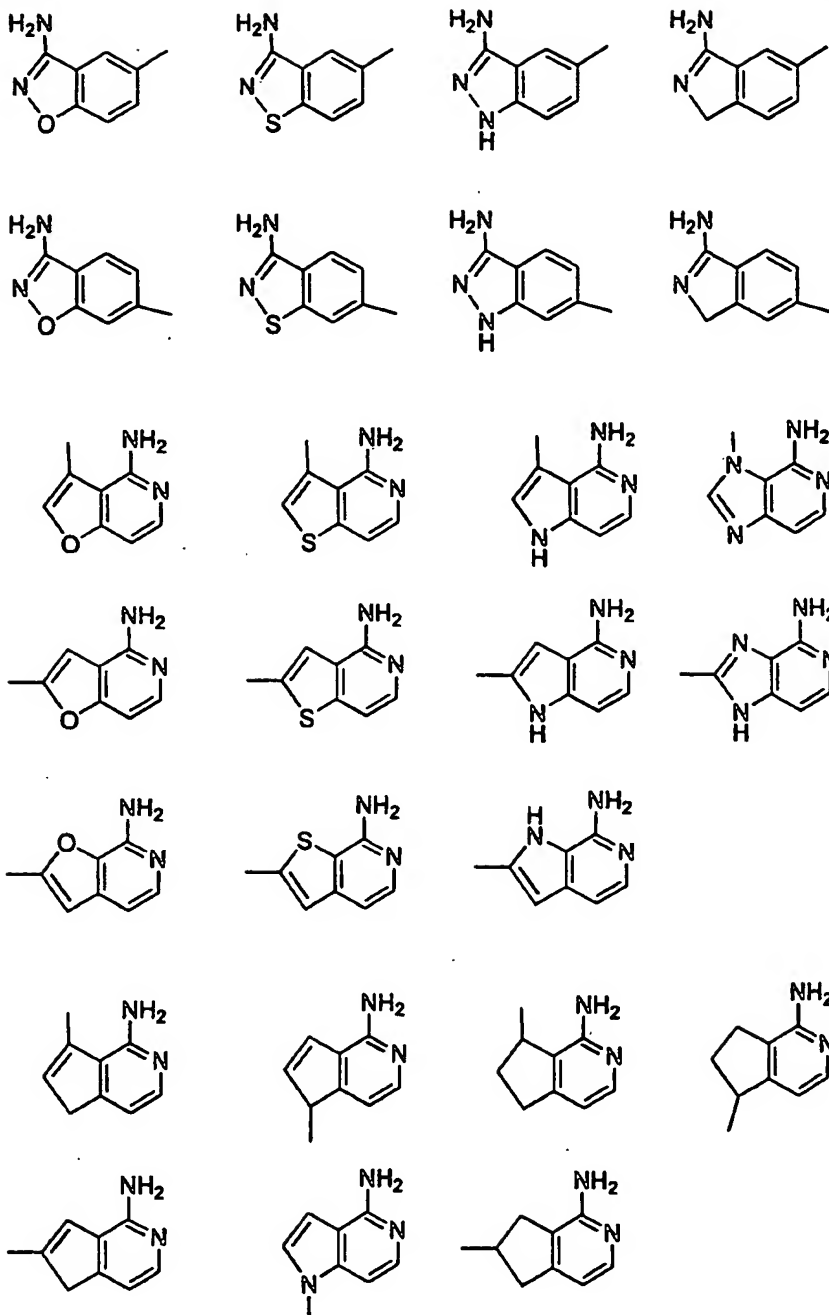
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5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from the group:



5

L_n is a linker which is absent or is selected from O, S, CH₂,
 *CH₂NHC(O), *CH(R^a)NHC(O), *CH₂NHC(O)CH₂, and
 *CH(R^a)NHC(O)CH₂, provided that L_n and M do not form an
 O-N or S-N bond and the * indicates where L_n is bonded
 to G;

10

M¹ is absent or is CHR;

M² is N or CR^f;

5

M³ is N or CR^d;

provided that only one of M² and M³ is N;

10 R^a is selected from C(O)C(O)OR³, C(O)C(O)NR²R^{2a}, and C(O)-A;

R^b is selected from H, R, phenyl, C₁₋₁₀ alkyl, and C₂₋₅
alkenyl;

15 R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are -(CH₂)₄-;

R^d is selected from H, F, and Cl;

20

R^e is selected from H, N(CH₃)(CH₂CO₂H) and S-(5-6 membered
aromatic heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O,
and S substituted with 0-2 R⁴);

25

alternatively, R^d and R^e combine to form -NR³-C(O)-C(R^{1b}R³)-
NR³- or -N=CR²-NR³-;

R^f is selected from H, F, and Cl;

30

alternatively, R^e and R^f combine to form -NR³-C(R^{1b}R³)-C(O)-
NR³- or -NR³-CR²=N-;

R^g is selected from H, CH₂OR³, CH₂C(O)OR³, C₁₋₄ alkyl,
35 C(O)NH₂, and NH₂;

R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $\text{CH}=\text{CH}$ -phenyl;

5 R^i is selected from $\text{SO}_2\text{CH}_2\text{C}(\text{O})\text{OR}^3$, $\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{OR}^3$, and $\text{C}(\text{O})\text{OR}^3$;

R is selected from H, Cl, F, Br, I, $(\text{CH}_2)_t\text{OR}^3$, C_{1-4} alkyl, benzyl, OCF_3 , CF_3 , $\text{C}(\text{O})\text{NR}^7\text{R}^8$, and $(\text{CR}^8\text{R}^9)_t\text{NR}^7\text{R}^8$;

10

Z is selected from a $(\text{CR}^8\text{R}^9)_{1-4}$, $(\text{CR}^8\text{R}^9)_r\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})(\text{CR}^8\text{R}^9)_r$,

15

$(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{OC}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_p(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_2(\text{CH}=\text{CH})$, $(\text{CCR}^8\text{R}^9)_r\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2(\text{CR}^8\text{R}^9)_r$, and $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, provided that Z does not form

20

a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with the groups to which Z is attached;

R^{1a} is absent or selected from $-(\text{CH}_2)_r\text{-R}^{1'}$, $-\text{CH}=\text{CH-R}^{1'}$,

$\text{NHCH}_2\text{R}^{1''}$, $\text{OCH}_2\text{R}^{1''}$, $\text{SCH}_2\text{R}^{1''}$, $\text{NH}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$,

25

$\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$;

$R^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, $-\text{CN}$, $-\text{CHO}$,

$(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OR}^2$, NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $\text{OC}(\text{O})\text{R}^2$,

$(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$, $\text{S}(\text{O})_p(\text{CH}_2)_r\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$,

30

$\text{C}(=\text{NR}^{2c})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$,

$\text{OC}(\text{O})\text{NR}^{2a}\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$,

NR²SO₂R^{2b}, C₃₋₆ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

5

R^{1''} is selected from H, CH(CH₂OR²)₂, C(O)R^{2c}, C(O)NR²R^{2a}, S(O)R^{2b}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

10 R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with A;

R², at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

20 R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ cycloalkylmethyl substituted with 0-2 R^{4b}, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

25 R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

30

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from

the group consisting of N, O, and S substituted with
0-2 R^{4b};

alternatively, R² and R^{2a}, together with the atom to which
they are attached, combine to form a 5 or 6 membered
saturated, partially saturated or unsaturated ring
substituted with 0-2 R^{4b} and containing from 0-1
additional heteroatoms selected from the group
consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and
phenyl;

A is selected from:

C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and
5-10 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O, and
S substituted with 0-2 R⁴;

A¹ is H or A;

alternatively, A and A¹ and the carbon to which they are
attached combine to form fluorene;

A² is selected from H, A, and CHA³A⁴;

A³ is selected from H, A, C₁₋₄ alkyl, and -(CH₂)_nNR²R^{2a};

A⁴ is H or A;

B is selected from: H, Y, and X-Y

5

X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -CR²(NR^{1''}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -OS(O)₂-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;

15

Y is selected from:

(CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,

C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and

20

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

25

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, C(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, C(O)NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, NHCH₂R^{1''}, OCH₂R^{1''}, SCH₂R^{1''}, N(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and S(CH₂)₂(CH₂)_tR^{1'};

alternatively, one R^4 is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

5

R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_r-F$, $(CH_2)_r-Br$, $(CH_2)_r-Cl$, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)R^{3c}$,
 10 $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $C(O)NHSO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle
 15 containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R^5 ;

R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$,
 20 $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;

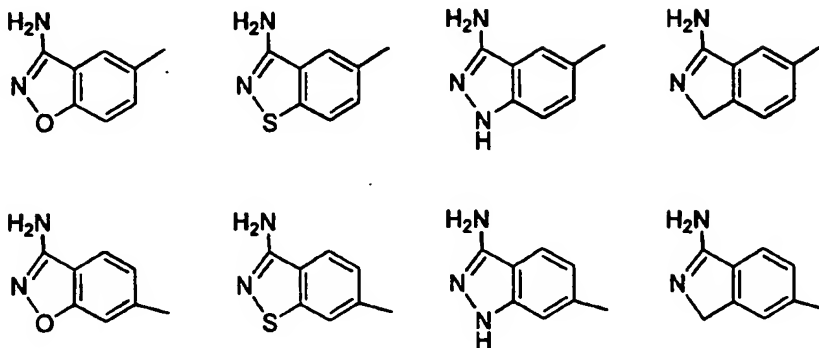
25 R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl substituted with 0-2 R^6 , and benzyl substituted with 0-2 R^6 ;

R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$,
 30 halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

- R⁷, at each occurrence, is selected from H, OH, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₄ alkoxycarbonyl, (CH₂)_n-phenyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxy carbonyl, C₆₋₁₀ arylmethylcarbonyl, C₁₋₄ alkylcarbonyloxy C₁₋₄ alkoxy carbonyl, C₆₋₁₀ arylcarbonyloxy C₁₋₄ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C₁₋₄ alkoxy carbonyl;
- 10 R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;
- alternatively, R⁷ and R⁸ combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional
15 heteroatoms selected from the group consisting of N, O, and S;
- R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;
- 20 R¹⁰ is selected from H, phenyl substituted with 0-2 R^{4a}, and naphthyl substituted with 0-2 R^{4a};
- n, at each occurrence, is selected from 0, 1, 2, and 3;
- 25 m, at each occurrence, is selected from 0, 1, and 2;
- p, at each occurrence, is selected from 0, 1, and 2;
- 30 r, at each occurrence, is selected from 0, 1, 2, and 3;
- s, at each occurrence, is selected from 0, 1, and 2; and,
- t, at each occurrence, is selected from 0, 1, 2, and 3.
- 35

[4] In a preferred embodiment, the present invention provides a novel compound, wherein:

5 G is selected from the group:



R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl,
 10 OCF_3 , CF_3 , $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

Z is selected from a CH_2O , OCH_2 , CH_2NH , $NHCH_2$, $C(O)$, $CH_2C(O)$,
 $C(O)CH_2$, $NHC(O)$, $C(O)NH$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH ,
 15 $NHSO_2$, provided that Z does not form a N-N, N-O,
 NCH_2N , or NCH_2O bond with ring M or group A;

A is selected from one of the following carbocyclic and
 heterocyclic systems which are substituted with 0-2 R^4 ;
 phenyl, piperidinyl, piperazinyl, pyridyl,
 20 pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,
 25 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,
 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
 benzothiofuranyl, indolyl, benzimidazolyl,

benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is selected from: H, Y, and X-Y;

5

X is selected from C₁₋₄ alkylene, -C(O)-, -C(=NR)-,

-CR²(NR²R^{2a})-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O), -C(O)NR²-,

-NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-,

-CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)NR²-, -NR²-,

10

-NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;

Y is NR²R^{2a} or CH₂NR²R^{2a}, provided that X-Y do not form a N-N or O-N bond;

15 alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,

20

1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,

25

1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,

1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,

1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

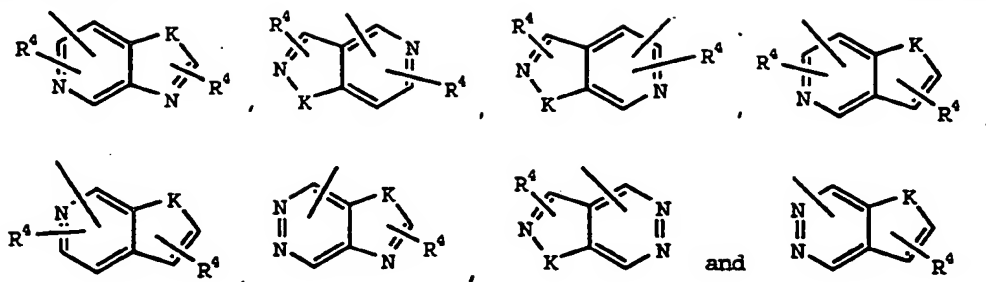
1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,

benzothiofuranyl, indolyl, benzimidazolyl,

30

benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:

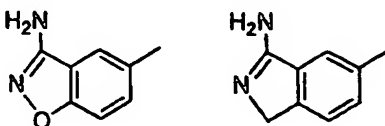


K is selected from O, S, NH, and N.

5

[5] In a more preferred embodiment, the present invention provides a novel compound, wherein:

G is selected from:



10

Z is C(O)CH₂ and CONH, provided that Z does not form a N-N bond with group A;

15 A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R⁴; and,

B is selected from Y, X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

20

B is selected from: Y and X-Y;

X is selected from CH₂, -C(O)-, and O;

25 Y is NR²R^{2a} or CH₂NR²R^{2a}, provided that X-Y does not form an O-N bond;

alternatively, Y is selected from one of the following
carbocyclic and heterocyclic systems which are
substituted with 0-2 R^{4a};

5 phenyl, piperazinyl, pyridyl, pyrimidyl,
morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-
triazolyl;

R², at each occurrence, is selected from H, CF₃, CH₃, benzyl,
and phenyl;

10

R^{2a}, at each occurrence, is selected from H, CF₃, CH₃,
CH(CH₃)₂, cyclopropylmethyl, benzyl, and phenyl;

alternatively, R² and R^{2a} combine to form a ring system
15 substituted with 0-2 R^{4b}, the ring system being selected
from pyrrolidinyl, piperazinyl and morpholino;

R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², Cl,
F, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;

20

R^{4a} is selected from Cl, F, C₁₋₄ alkyl, CF₃, (CH₂)_rNR²R^{2a},
S(O)_pR⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

R^{4b}, at each occurrence, is selected from OH, Cl, F, CH₃, and
25 CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl, and benzyl;

30 R⁷, at each occurrence, is selected from H, CH₃, and CH₂CH₃;
and,

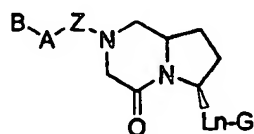
R⁸, at each occurrence, is selected from H and CH₃.

[6] In an even further preferred embodiment, the present invention provides a novel compound, wherein:

- 5 A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,
- 10 B is selected from the group: 2-CF₃-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-
- 15 (isopropylaminomethyl)phenyl, 2-(cyclopropylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 2-(3-hydroxy-N-pyrrolidinylmethyl)phenyl, 4-morpholino, 2-(1'-CF₃-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 1-methyl-2-
- 20 imidazolyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-(N,N-dimethylaminomethyl)imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

25

[7] In another even more preferred embodiment, the present invention provides a compound of formula:



30

L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂, the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OR³;

35

Z is selected from a C₁₋₄ alkylene, (CH₂)_rC(O), and
(CH₂)_rS(O)₂;

5 R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

10 R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃,
CH₃, benzyl, and phenyl;

15 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

A is C₅₋₆ carbocyclic residue substituted with 0-2 R⁴;

20 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

25 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

30 r, at each occurrence, is selected from 0, 1, 2, and 3.

[8] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH(R^a)NHC(O)CH_2$;

5

R^a is $C(O)C(O)OH$;

Z is selected from a CH_2 , $(CH_2)_2C(O)$, and $CH_2S(O)_2$;

10 A is cyclohexyl or phenyl and is substituted with 0-1 R^4 ;

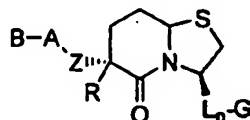
R^4 , at each occurrence, is selected from H , $=O$, OR^2 , CH_2OR^2 , F , Cl , Br , I , C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

15

r , at each occurrence, is selected from 0, 1, and 2.

[9] In another even more preferred embodiment, the present invention provides a compound of formula:

20



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the $*$ indicates
25 where L_n is bonded to G ;

R^a is $C(O)C(O)OR^3$;

R is H or NH_2 ;

30

Z is selected from a C_{1-4} alkylene, $(CH_2)_rC(O)$, and $(CH_2)_rS(O)_2$;

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

10 R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

15

A is a C₅₋₆ carbocyclic residue substituted with 0-2 R⁴;

20 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

25

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

30

[10] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is *CH(R^a)NHC(O)CH₂;

R is H;

R^a is C(O)C(O)OH;

5

Z is selected from a CH₂, (CH₂)₂C(O), and CH₂S(O)₂;

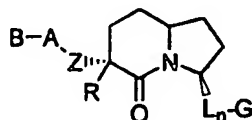
A is cyclohexyl or phenyl and is substituted with 0-1 R⁴;

10 R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

r, at each occurrence, is selected from 0, 1, 2, and 3.

15

[11] In another even more preferred embodiment, the present invention provides a compound of formula:



20

L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂, the * indicates
where L_n is bonded to G;

25 R is H or NH₂;

R^a is C(O)C(O)OR³;

Z is C₁₋₄ alkylene;

30

R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

10 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is phenyl substituted with 0-2 R⁴;

15 R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

20 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

25

[12] In another still more preferred embodiment, the present invention provides a compound wherein:

30 L_n is *CH(R^a)NHC(O)CH₂;

R is NH₂;

R^a is C(O)C(O)OH;

35

Z is CH₂;

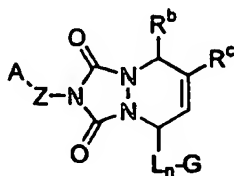
A is phenyl substituted with 0-1 R⁴;

5 R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

10

[13] In another even more preferred embodiment, the present invention provides a compound of formula:



15

L_n is *CH₂NHC(O) or *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

R^a is selected from C(O)C(O)OR³ and C(O)-A;

20

R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

R^c is selected from H and C₁₋₆ alkyl;

25 alternatively, R^b and R^c together are -(CH₂)₄-;

Z is (CR⁸R⁹)₁₋₄;

R², at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

30

R^{2a}, at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

5 R^{2b}, at each occurrence, is selected from H, CF₃, and C₁₋₆ alkyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

10 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

C₆₋₁₀ aromatic carbocyclic residue substituted with 0-2

15 R⁴, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

20 R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

25 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

30 R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

[14] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH(R^a)NHC(O)$ and the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OH$ or $C(O)-(benzothiazol-2-yl)$;

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8H)_{1-2}$;

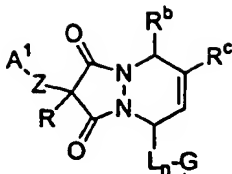
A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R^4 ;

R^4 , at each occurrence, is selected from H, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

R^8 , at each occurrence, is selected from H, methyl and phenyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

[15] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the $*$ indicates where L_n is bonded to G;

5 R^a is selected from $C(O)C(O)OR^3$ and $C(O)-A$;

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

10

alternatively, R^b and R^c together are $-(CH_2)_4-$;

R is selected from H, benzyl, C_{1-4} alkyl, and NH_2 ;

15 Z is $(CR^8R^9)_{1-4}$;

R^2 , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

20 R^{2a} , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

R^{2b} , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

25

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

30 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

- C₆₋₁₀ aromatic ring substituted with 0-2 R⁴, and
5-10 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
5 N, O, and S substituted with 0-2 R⁴;

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl,
Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

10

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl, and benzyl;

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and
15 phenyl;

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and
phenyl;

20

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

25 [16] In another still more preferred embodiment, the present
invention provides a compound wherein:

L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to
G;

30

R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);

R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

35

R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8H)_{1-2}$;

5

A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R^4 ;

R^4 , at each occurrence, is selected from H, OR^2 , CH_2OR^2 , F,

10 Cl, Br, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$,

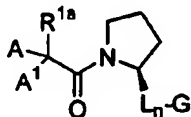
$(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and phenyl;

15

r, at each occurrence, is selected from 0, 1, and 2.

[17] In another even more preferred embodiment, the present
20 invention provides a compound of formula:



L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the * indicates where
 L_n is bonded to G;

25

R^{1a} is selected from $-(CH_2)_r-R^{1'}$ and $NHCH_2R^{1''}$;

$R^{1'}$ is selected from H, OR^2 , NR^2R^{2a} , and $NR^2SO_2(CH_2)_rR^{2b}$;

30 $R^{1''}$ is selected from $C(O)NR^2R^{2a}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

5 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from C₁₋₄ alkoxy, C₁₋₆
alkyl, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6
10 membered heterocyclic system containing from 1-2
heteroatoms selected from the group consisting of N, O,
and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃,
CH₃, benzyl, and phenyl;

15 alternatively, R² and R^{2a}, together with the atom to which
they are attached, combine to form a 5 or 6 membered
saturated, partially saturated or unsaturated ring
substituted with 0-2 R^{4b} and containing from 0-1
20 additional heteroatoms selected from the group
consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

25 A is phenyl substituted with 0-2 R⁴;

A¹ is H or A;

30 alternatively, A and A¹ and the carbon to which they are
attached combine to form fluorene;

A² is selected from H, A, and CHA³A⁴;

35 A³ is selected from H, A, C₁₋₄ alkyl, and -(CH₂)_nNR²R^{2a};

A' is H or A;

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl,
5 Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

R^{4b}, at each occurrence, is selected from H, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
10 (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵,
and CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl, and benzyl;

15

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

20

[18] In another still more preferred embodiment, the present
invention provides a compound wherein:

L_n is *CH₂NHC(O) and the * indicates where L_n is bonded to G;

25

R^{1a} is selected from -(CH₂)_r-R^{1'} and NHCH₂R^{1''};

R^{1'} is selected from OH, NR²R^{2a}, and NR²SO₂(CH₂)_rR^{2b};

30 R^{1''} is selected from C(O)NR²R^{2a}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, phenyl substituted with 0-1 R^{4b}, and pyrrolidinyl substituted with 0-1 R^{4b};

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

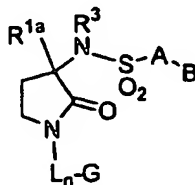
alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a piperidine ring substituted with 0-1 R^{4b};

R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R^{4b}, at each occurrence, is selected from H, =O, OH, F, Cl, C₁₋₄ alkyl, and NH₂; and,

r, at each occurrence, is selected from 0, 1, and 2.

[19] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is CH₂;

R^{1a} is -(CH₂)_r-R^{1'};

$R^{1'}$ is selected from H, C_{1-3} alkyl, $(CH_2)_rOR^2$, NR^2R^{2a} ,
C(O) R^{2c} , phenyl substituted with 0-2 R^4 , and 5-6
membered aromatic heterocyclic system containing from
5 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^4 ;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

10

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

R^{2b} , at each occurrence, is selected from H, C_{1-6} alkyl,
15 benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 ,
 CH_3 , benzyl, and phenyl;

20 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and
phenyl;

A is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^4 , and
25 5-10 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^4 ;

B is selected from: H, Y, and X-Y

30

X is selected from C_{1-4} alkylene, $-NR^2-$, and O;

Y is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^{4a} , and

0-2 R⁴, 6-azabenzothienyl substituted with 0-2 R⁴, and quinolinyl substituted with 0-2 R⁴;

B is selected from: H, Y, and X-Y

5

X is O;

Y is phenyl substituted with 0-1 R^{4a};

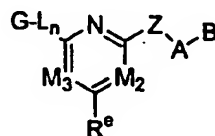
10 R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃;

R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F, 15 Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

20

[21] In another even more preferred embodiment, the present invention provides a compound of formula:



25 L_n is 0 or S;

M² is N or CR^f;

M³ is N or CR^d;

30

provided that only one of M² and M³ is N;

R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

5

R^d is selected from H, F, and Cl;

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1b}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

10

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1b}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

15

Z is O, provided that Z does not form a N-O or NCH_2O bond with the groups to which Z is attached;

R^{1b} is selected from H, C_{1-6} alkyl, and C_{1-6} alkyl substituted with A;

20

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

25 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

30

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

35

A is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R⁴, and
5 5-6 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O, and
S substituted with 0-2 R⁴;

B is H or Y;

10 Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and
5-6 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O, and
S substituted with 0-2 R^{4a};

15

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

20

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
(CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, Cl, Br, F, I, C₁₋₄ alkyl,
-CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b},
C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, and
25 CF₃; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

30 [22] In another still more preferred embodiment, the present
invention provides a compound wherein:

L_n is 0;

R^e is $N(CH_3)(CH_2CO_2H)$;

R^d is H or F;

5 alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1b}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

R^f is H or F;

10 alternatively, R^e and R^f combine to form $-NR^3-C(R^{1b}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

R^{1b} is selected from H, C_{1-2} alkyl and benzyl;

15 A is phenyl substituted with 0-2 R^4 ;

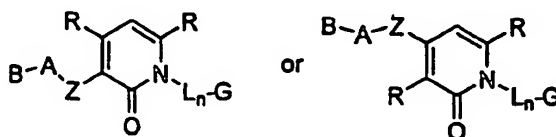
B is H or Y;

20 Y is 5 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

R^4 , at each occurrence, is selected from H, C_{1-4} alkyl, and NR^2R^{2a} ; and,

25 R^{4a} , at each occurrence, is selected from H, C_{1-4} alkyl, and NR^2R^{2a} .

30 [23] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the $*$ indicates
where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

5

R, at each occurrence, is selected from H, Cl, F, Br, I,
 OR^3 , C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

Z is selected from a C_{1-4} alkylene and $(CH_2)_rSO_2NR^3$;

10

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

15

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 ,
 CH_3 , benzyl, and phenyl;

20 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and
phenyl;

A is selected from:

25 C_{5-6} carbocyclic residue substituted with 0-2 R^4 , and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^4 ;

B is selected from: H, Y, and X-Y

30

alternatively, when B is H, A is $(phenyl)_2CH-$ substituted
with 0-2 R^4 ;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-NR^2-$, and O;

35

Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
5 N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

10

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

15 r, at each occurrence, is selected from 0, 1, 2, and 3.

[24] In another still more preferred embodiment, the present
invention provides a compound wherein:

20

L_n is *CH₂NHC(O)CH₂ and the * indicates where L_n is bonded to
G;

R, at each occurrence, is selected from H and C₁₋₄ alkyl;

25

Z is CH₂SO₂NR³;

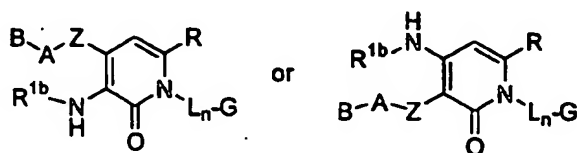
A is phenyl substituted with 0-2 R⁴;

30 B is H;

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl,
C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, and C(O)NR²R^{2a};
and,

r, at each occurrence, is selected from 0, 1, and 2.

- 5 [25] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates
10 where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

R, at each occurrence, is selected from H, C_{1-4} alkyl, and
15 NH_2 ;

R^{1b} is H or C_{1-6} alkyl;

Z is selected from a C_{1-4} alkylene and $(CH_2)_rS(O)_p(CH_2)_r$;
20

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl,
25 benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 ,
 CH_3 , benzyl, and phenyl;

30 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and
phenyl;

A is selected from:

C₃₋₆ carbocyclic residue substituted with 0-2 R⁴, and
5 5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R⁴;

B is selected from: H, Y, and X-Y

alternatively, when B is H, A is (phenyl)₂CH- substituted
10 with 0-2 R⁴;

X is selected from C₁₋₄ alkylene, -C(O)-, -NR²-, and O;

Y is selected from:

15 C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a};

20 alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

25

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

30 p is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[26] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $^*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R is H or C_{1-4} alkyl;

R^{1b} is H;

Z is CH_2 , CH_2S , or $CH_2S(O)_2$;

A is a C_{3-6} carbocyclic residue substituted with 0-2 R^4 ;

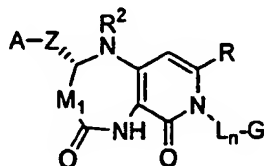
B is H

alternatively, Z-A-B combine to form $S-C_{1-6}$ alkyl;

R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

r, at each occurrence, is selected from 0, 1, and 2.

[27] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $^*CH_2NHC(O)CH_2$ or $^*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

M¹ is absent or is CHR;

R is selected from H, Cl, F, Br, I, OR³, C₁₋₄ alkyl, OCF₃,
CF₃, and NH₂;

5

Z is C₁₋₄ alkylene;

R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

10

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

15

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃,
CH₃, benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

20 A is selected from:

C₃₋₆ carbocyclic residue substituted with 0-2 R⁴, and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R⁴;

25

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl,
Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

30 r, at each occurrence, is selected from 0, 1, 2, and 3.

[28] In another still more preferred embodiment, the present
invention provides a compound wherein:

35

L_n is $*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

M^1 is absent;

5

R is selected from H and C_{1-4} alkyl;

Z is CH_2 ;

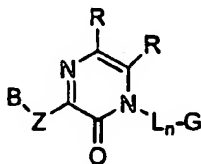
10 A is C_{3-6} carbocyclic residue substituted with 0-1 R^4 ;

R^4 , at each occurrence, is selected from H, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and CF_3 ; and,

15 r, at each occurrence, is selected from 0, 1, and 2.

[29] In another even more preferred embodiment, the present invention provides a compound of formula:

20



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

25 R^a is $C(O)C(O)OR^3$;

R, at each occurrence, is selected from H, Cl, F, Br, I, OR^3 , C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

30 Z is $(CHR^8)NR^3$, $(CHR^8)_2NR^3$, and $(CHR^8)_2SO_2R^3$;

provided that when Z is $(CHR^8)_2NR^3$, then B is absent;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

5 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

10

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

15 R^{3a} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

B is H or Y;

Y is selected from:

20 C_{5-6} carbocyclic residue substituted with 0-2 R^{4a} , and 5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

25 R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

30 R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and phenyl; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[30] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $^*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to
5 G;

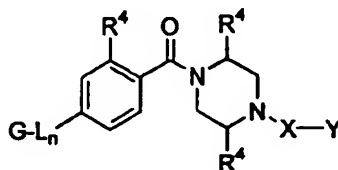
R, at each occurrence, is selected from H and C₁₋₄ alkyl;

Z is $(CH_2)_2NR^3$, $(CHR^8)_2NR^3$ or $(CHR^8)_2SO_2R^3$;
10 B is H or Y;

Y is phenyl substituted with 0-1 R⁴, pyridyl substituted
with 0-1 R⁴ or N-morpholino substituted with 0-1 R⁴;
15 R⁴, at each occurrence, is selected from H, and C₁₋₄ alkyl;

R⁸, at each occurrence, is selected from H, methyl and
phenyl; and,
20 r, at each occurrence, is selected from 0, 1, and 2.

[31] In another even more preferred embodiment, the present
25 invention provides a compound of formula:



L_n is absent;

30 R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 ,
5 CH_3 , benzyl, and phenyl;

X is SO_2 or $SO_2(CH=CH)$;

Y is selected from:

10 C_{6-10} carbocyclic residue substituted with 0-2 R^{4a} , and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a} ;

15 R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 ,
F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$,
 $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

R^{4a} , at each occurrence, is selected from H, OR^2 , CH_2OR^2 , F,
20 Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$,
 $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

25

[32] In another still more preferred embodiment, the present
invention provides a compound wherein:

X is SO_2 ;

30

Y is selected from phenyl substituted with 0-2 R^{4a} and
naphthyl substituted with 0-2 R^{4a} ;

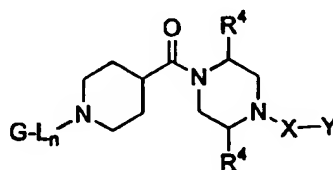
R^4 , at each occurrence, is selected from H, =O, OH, CH₂OH, F, Cl, Br, C₁₋₄ alkyl, C(O)NR²R^{2a}, and C(O)R^{2c};

R^{4a} , at each occurrence, is selected from H, OH, CH₂OH, F,

5 Cl, Br, C₁₋₄ alkyl, and C(O)R^{2c}; and,

r, at each occurrence, is selected from 0, 1, and 2.

10 [33] In another even more preferred embodiment, the present invention provides a compound of formula:



15 L_n is absent;

R^2 , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

20 R^{2a} , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

25

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

30

X is SO₂ or SO₂(CH=CH);

Y is selected from:

C₆₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
5 5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
10 C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F,
Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

15

r, at each occurrence, is selected from 0, 1, 2, and 3.

[34] In another still more preferred embodiment, the present
20 invention provides a compound wherein:

X is SO₂;

Y is phenyl substituted with 0-2 R^{4a} or naphthyl substituted
25 with 0-2 R^{4a};

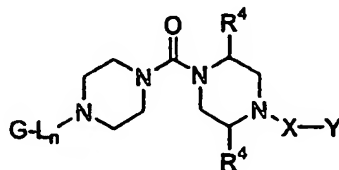
R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, NH₂, (CH₂)_rC(O)R^{2c}, and
C(O)NR²R^{2a};

30

R^{4a}, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, NH₂, (CH₂)_rC(O)R^{2c}, and
C(O)NR²R^{2a};

r, at each occurrence, is selected from 0, 1, 2, and 3.

[35] In another even more preferred embodiment, the present
5 invention provides a compound of formula:



L_n is absent;

10 R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

15

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

alternatively, R^2 and R^{2a} , together with the atom to which
20 they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

25 X is SO_2 or $SO_2(CH=CH)$;

Y is selected from:

C_{6-10} carbocyclic residue substituted with 0-2 R^{4a} , and
5-6 membered aromatic heterocyclic system containing
30 from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

5 R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

r, at each occurrence, is selected from 0, 1, 2, and 3.

10

[36] In another still more preferred embodiment, the present invention provides a compound wherein:

15 X is SO₂;

Y is phenyl substituted with 0-2 R^{4a} or naphthyl substituted with 0-2 R^{4a};

20 R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, NH₂, (CH₂)_rC(O)R^{2c}, and C(O)NR²R^{2a};

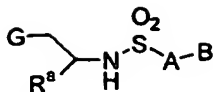
R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, NH₂, (CH₂)_rC(O)R^{2c}, and C(O)NR²R^{2a}; and,

25

r, at each occurrence, is selected from 0, 1, and 2.

30

[37] In another even more preferred embodiment, the present invention provides a compound of formula:



R^a is C(O)-(6 membered heterocyclic system containing 1 N atom and substituted with 0-2 R^4);

5

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

10

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

20

A is a 10 membered bicyclic heterocyclic system containing 1 N atom and substituted with 0-2 R^4 ;

B is H or Y;

25

Y is selected from:

C_{3-6} carbocyclic residue substituted with 0-2 R^{4a} , and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

30

R^4 , at each occurrence, is selected from H, =O, OR^2 , F, Cl, Br, I, C_{1-4} alkyl, NR^2R^{2a} , $(CH_2)_x C(O)R^{2c}$, $C(O)NR^2R^{2a}$, and CF_3 ;

R^{4a} , at each occurrence, is selected from H, =O, OR^2 , F, Cl, Br, I, C_{1-4} alkyl, NR^2R^{2a} , $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, and CF_3 ;

5

r , at each occurrence, is selected from 0, 1, 2, and 3.

[38] In a still more preferred embodiment, the present invention provides a compound wherein:

R^a is $C(O)-(N-1,2,3,6\text{-tetrahydropyridine substituted with } CO_2H)$;

15 alternatively R^a is $C(O)-(N-1,2,3,6\text{-tetrahydropyridine substituted with } CH_3)$;

A is 1,2,3,4-tetrahydroisoquinoline substituted with 1-2 R^4 ;

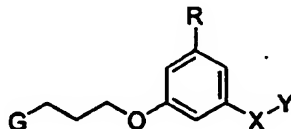
20 B is H;

R^4 , at each occurrence, is selected from H, methyl, =O, OR^2 , F, Cl, Br, I, C_{1-4} alkyl, NR^2R^{2a} , $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

25

r , at each occurrence, is selected from 0, 1, and 2.

[39] In another even more preferred embodiment, the present invention provides a compound of formula:



R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

10 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

15

X is OSO₂;

Y is selected from:

20 C₆₋₁₀ aromatic ring substituted with 0-2 R^{4a}, and 5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R⁴ is H;

25

R^{4a}, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

30 r, at each occurrence, is selected from 0, 1, 2, and 3.

[40] In a still more preferred embodiment, the present invention provides a compound wherein:

35

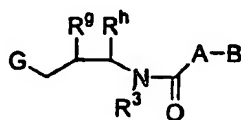
R is methyl;

Y is selected from phenyl substituted with 0-2 R^{4a} , naphthyl substituted with 0-2 R^{4a} , and quinolinyl substituted with 0-2 R^{4a} ;

R^{4a} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and CF_3 ; and,

r, at each occurrence, is selected from 0, 1, and 2.

[41] In another more preferred embodiment, the present invention provides a compound of formula:



R^g is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^4 , and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

15

B is H or Y;

Y is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^{4a} , and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

R^{4a} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

- 5 [42] In a still more preferred embodiment, the present invention provides a compound wherein:

R^g is selected from CH₂OR³, and CH₂C(O)OCH₃;

- 10 R^h is selected from CH₂-phenyl, CH₂CH₂-phenyl, and CH=CH-phenyl;

A is phenyl;

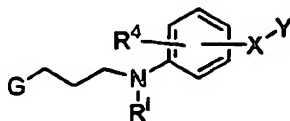
- 15 B is Y;

Y is phenyl substituted with 0-2 R^{4a};

- 20 R^{4a}, at each occurrence, is selected from H, OR², Cl, Br, F, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

- 25 [43] In another more preferred embodiment, the present invention provides a compound of formula:



- 30 Rⁱ is selected from SO₂CH₂C(O)OR³, C(O)CH₂C(O)OR³, and C(O)OR³;

X is O;

Y is pyrrolidinyl substituted with 1-2 R^{4a} or piperidinyl substituted with 1-2 R^{4a};

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R⁴, at each occurrence, is selected from H, F, Cl, Br, I, C₁₋₄ alkyl, NR²R^{2a}, and CF₃; and,

R^{4a}, at each occurrence, is selected from H, C₁₋₄ alkyl, CH₂NR²R^{2a}, and C(=NR²)CH₃.

[44] In a still more preferred embodiment, the present invention provides a compound wherein:

Rⁱ is selected from SO₂CH₂C(O)OR³ and C(O)CH₂C(O)OR³;

Y is piperidinyl substituted with 1-2 R^{4a};

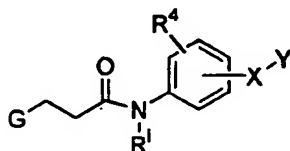
R³, at each occurrence, is selected from H and C₁₋₄ alkyl;

R⁴ is H; and,

R^{4a}, at each occurrence, is selected from H, C₁₋₄ alkyl, CH₂NR²R^{2a}, and C(=NR²)CH₃.

5

[45] In another more preferred embodiment, the present invention provides a compound of formula:



R¹ is selected from SO₂CH₂C(O)OR³, C(O)CH₂C(O)OR³, and
10 C(O)OR³;

X is O;

Y is pyrrolidinyl substituted with 1-2 R^{4a} or piperidinyl
15 substituted with 1-2 R^{4a};

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

20 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered
25 saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
30 phenyl;

R⁴, at each occurrence, is selected from H, F, Cl, Br, I,
C₁₋₄ alkyl, NR²R^{2a}, and CF₃; and,

R^{4a}, at each occurrence, is selected from H, C₁₋₄ alkyl,
5 CH₂NR²R^{2a}, and C(=NR²)CH₃.

[46] In a still more preferred embodiment, the present
invention provides a compound wherein:

10

Rⁱ is selected from SO₂CH₂C(O)OR³ and C(O)CH₂C(O)OR³;

Y is piperidinyl substituted with 1-2 R^{4a};

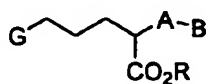
15 R³, at each occurrence, is selected from H and C₁₋₄ alkyl;

R⁴ is H; and,

R^{4a}, at each occurrence, is selected from H, C₁₋₄ alkyl,
20 CH₂NR²R^{2a}, and C(=NR²)CH₃.

[47] In another more preferred embodiment, the present
invention provides a compound of formula:

25



R is selected from H, C₁₋₄ alkyl, and NH₂;

30 R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

10

A is selected from:

C₆₋₁₀ aromatic ring substituted with 0-2 R⁴, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of

15 N, O, and S substituted with 0-2 R⁴;

B is Y or X-Y;

X is O;

20

Y is selected from phenyl substituted with 0-2 R^{4a}, pyrrolidinyl substituted with 0-2 R^{4a}, and piperidinyl substituted with 0-2 R^{4a};

25 R⁴, at each occurrence, is selected from H, OH, CH₂OH, Cl, Br, F, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃;

R^{4a}, at each occurrence, is selected from H, OH, CH₂OH, Cl, Br, F, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a},
30 C(=NR²)NR²R^{2a}, and CF₃;

n is 0 or 1; and,

35 r, at each occurrence, is selected from 0, 1, 2, and 3.

[48] In a still more preferred embodiment, the present invention provides a compound wherein:

5

R is selected from H, methyl, ethyl, and NH_2 ;

A is phenyl substituted with 0-1 R^4 or thienyl substituted with 0-1 R^4 ;

10

B is Y or X-Y;

X is O;

15 Y is selected from phenyl substituted with 0-2 R^{4a} , pyrrolidinyl substituted with 0-2 R^{4a} , and piperidinyl substituted with 0-2 R^{4a} ;

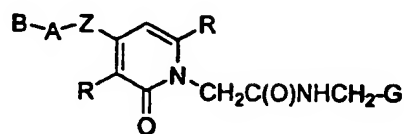
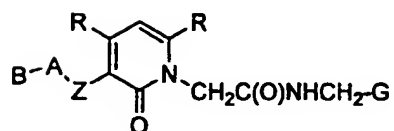
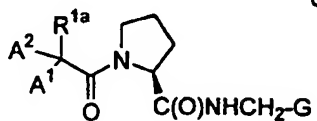
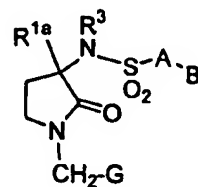
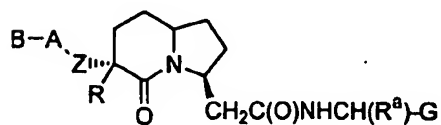
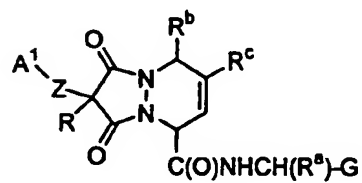
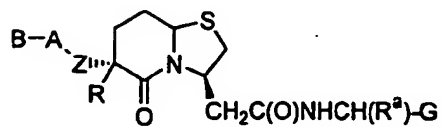
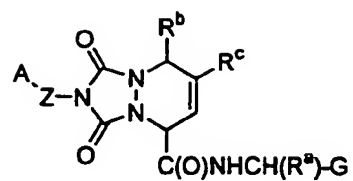
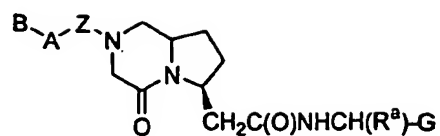
20 R^4 , at each occurrence, is selected from H, OH, CH_2OH , Cl, Br, F, I, C_{1-4} alkyl, NH_2 , $\text{C}(\text{O})\text{NH}_2$, and CF_3 ;

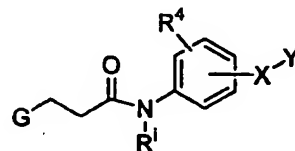
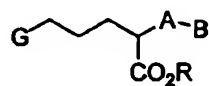
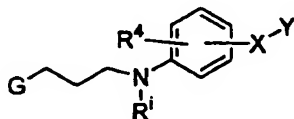
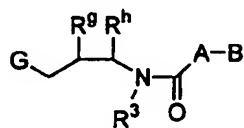
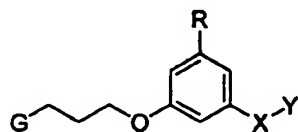
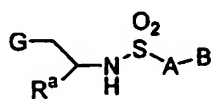
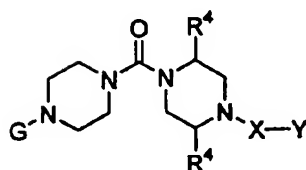
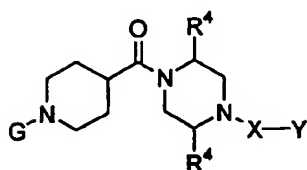
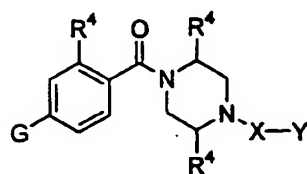
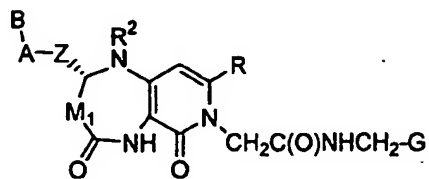
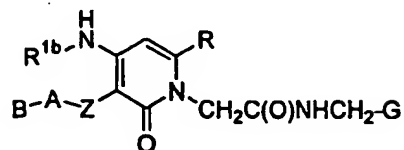
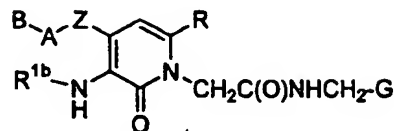
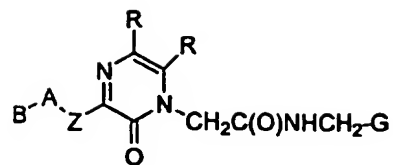
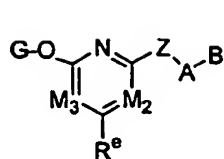
R^{4a} , at each occurrence, is selected from H, OH, CH_2OH , Cl, Br, F, I, C_{1-4} alkyl, NH_2 , and $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$; and,

25 r, at each occurrence, is selected from 0, 1, 2, and 3.

[49] In another embodiment, the present invention provides compounds selected from the group:

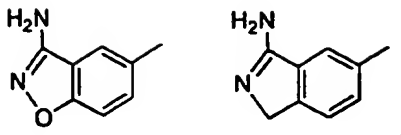
30





5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from:



R^a is selected from $C(O)C(O)OH$ and $C(O)(\text{benzothiazol-2-yl})$;

5 R^g is selected from H , CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

R^h is selected from H , CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

10

R^i is selected from $SO_2CH_2C(O)OH$ and $C(O)CH_2C(O)OH$, and $C(O)OR^3$;

15

R , at each occurrence, is selected from H , methyl, ethyl, benzyl, and NH_2 ;

R^2 , at each occurrence, is selected from H , CF_3 , CH_3 , benzyl, and phenyl;

20

R^{2a} , at each occurrence, is selected from H , CF_3 , CH_3 , benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;

25

R^3 , at each occurrence, is selected from H , C_{1-4} alkyl, and phenyl;

Z is $C(O)CH_2$ or $CONH$;

30

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4 ; and,

B is selected from Y, X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

5 R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;

R^{4a} is selected from C₁₋₄ alkyl, CF₃, S(O)₂R⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

10

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

X is CH₂ or C(O);

15

Y is selected from NR²R^{2a} and CH₂NR²R^{2a};

p is selected from 0, 1, and 2; and,

20 r is selected from 0, 1, and 2.

In another embodiment, the present invention provides novel pharmaceutical compositions, comprising: a
25 pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of present invention or a pharmaceutically acceptable salt form thereof.

30 In another embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt
35 form thereof.

In another embodiment, the present invention provides novel compounds for use in therapy.

5

In another embodiment, the present invention provides the use of novel compounds for the manufacture of a medicament for the treatment of thrombosis or a disease mediated by factor Xa.

10

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6 , then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-10} alkyl (or alkylene), is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , and C_{10} alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$). Examples of

haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

"Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen

5 bridge. C₁₋₁₀ alkoxy, is intended to include C₁, C₂, C₃, C₄,

C₅, C₆, C₇, C₈, C₉, and C₁₀ alkoxy groups. Examples of

alkoxy include, but are not limited to, methoxy, ethoxy,

n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy,

n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to

10 include saturated ring groups, such as cyclopropyl,

cyclobutyl, or cyclopentyl. C₃₋₇ cycloalkyl, is intended to

include C₃, C₄, C₅, C₆, and C₇ cycloalkyl groups. "Alkenyl"

or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or

15 more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl.

C₂₋₁₀ alkenyl (or alkenylene), is intended to include C₂, C₃,

C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkenyl groups. "Alkynyl" or

"alkynylene" is intended to include hydrocarbon chains of

20 either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable

point along the chain, such as ethynyl and propynyl. C₂₋₁₀

alkynyl (or alkynylene), is intended to include C₂, C₃, C₄,

C₅, C₆, C₇, C₈, C₉, and C₁₀ alkynyl groups.

25 "Halo" or "halogen" as used herein refers to fluoro,

chloro, bromo, and iodo; and "counterion" is used to

represent a small, negatively charged species such as

chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic group" is

30 intended to mean any stable 3, 4, 5, 6, or 7-membered

monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or

13-membered bicyclic or tricyclic, any of which may be

saturated, partially unsaturated, or aromatic. Examples of

such carbocycles include, but are not limited to,

35 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane,

[4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or

5 "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently
10 selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group
15 at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the
20 total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended
25 to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heterotams independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S
30 and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl,
35 benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-

dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the

parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications

are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like. Preferred prodrugs are amidine prodrugs wherein D is $C(=NR^7)NH_2$ or its tautomer $C(=NH)NHR^7$ and R^7 is selected from OH, C_{1-4} alkoxy, C_{6-10} aryloxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, and C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl. More preferred prodrugs are where R^7 is OH, methoxy, ethoxy, benzyloxycarbonyl, methoxycarbonyl, and methylcarbonyloxymethoxycarbonyl.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

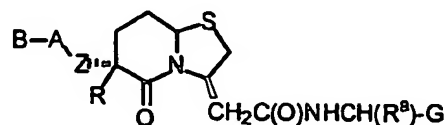
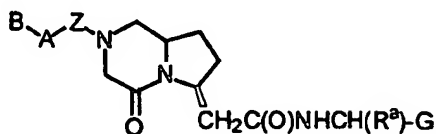
"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit factor Xa or thrombin or treat diseases related to factor Xa or thrombin in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* 22:27-55 (1984), occurs when the effect (in this case, inhibition of factor Xa or thrombin) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of th

compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

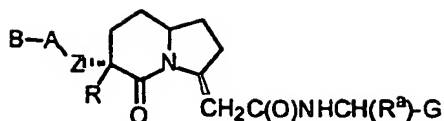
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SYNTHESIS

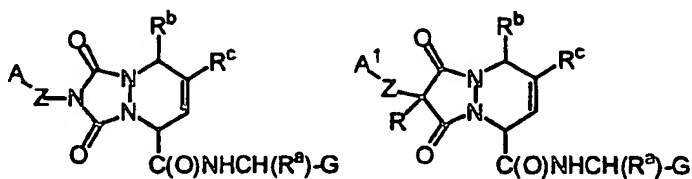
The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry; or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.



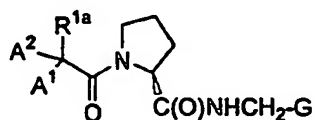
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Compounds of the above formulas can be prepared by coupling corresponding acid and amine precursors. The acid precursors can be prepared as shown in WO98/28326, WO 98/09987, WO /28326, WO96/19483, and WO98/05333, the contents of which are incorporated herein by reference. The G-CH(R^a)NH₂ precursors can be prepared as shown in the above-identified publications or as shown in the present application.

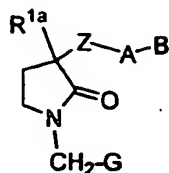


Compounds of the above formulas can be prepared by coupling corresponding acid and amine precursors. The acid precursors can be prepared as shown in WO98/05333, the contents of which are incorporated herein by reference. The G-CH(R^a)NH₂ precursors can be prepared as shown in the above-identified publications or as shown in the present application.

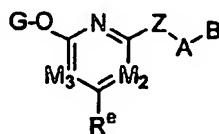


Compounds of the above formula can be prepared by coupling the corresponding acid and amine precursors. The acid precursors can be prepared as shown in U.S. Patent No. 5,798,377, the contents of which are incorporated herein by reference. The G-CH₂NH₂ precursors can be prepared as shown

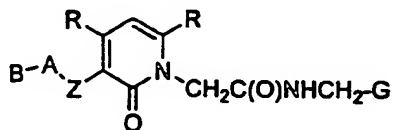
in the above-identified publication or as shown in the present application.



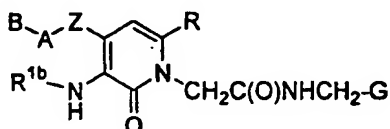
- 5 Compounds of the above formulas can be prepared by coupling corresponding G-CH₂NH₂ and ester-aldehyde precursors. The ester-aldehyde precursors can be prepared as shown in WO 98/05333, the contents of which are incorporated herein by reference. The G-CH₂NH₂ precursors
- 10 can be prepared as shown in the above-identified publication or as shown in the present application.



- 15 Compounds of the above formula can be prepared by coupling corresponding G-leaving group and alcohol-pyridyl or thiol-pyridyl precursors. The alcohol and thio precursors can be prepared as shown in U.S. Patent No. 5,693,641, WO96/28427, WO97/29067, WO98/07725, and
- 20 WO98/15547, the contents of which are incorporated herein by reference. The G-leaving group precursors can be prepared as shown in the above-identified publications or as shown in the present application. Alternatively, the compounds of the above formula can be prepared by displacing a leaving
- 25 group from the pyridyl precursor with the corresponding G-OH precursor. Leaving groups for this type of coupling can be SCH₃ or SO₂CH₃.

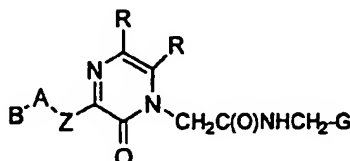


Compounds of the above formula can be prepared by coupling corresponding acid and amine precursors. The acid precursors can be prepared as shown in WO97/30708, the contents of which are incorporated herein by reference. The G-CH₂NH₂ precursors can be prepared as shown in the above-identified publication or as shown in the present application.



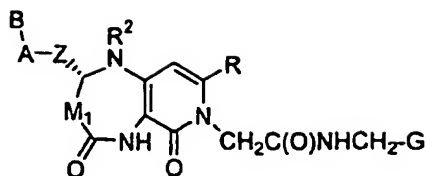
10

Compounds of the above formula can be prepared by coupling corresponding acid and amine precursors. The acid precursors can be prepared as shown in WO98/31670, the contents of which are incorporated herein by reference. The G-CH₂NH₂ precursors can be prepared as shown in the above-identified publication or as shown in the present application.

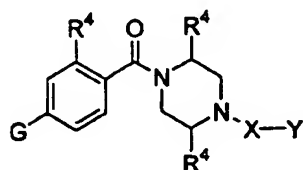


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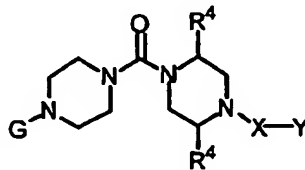
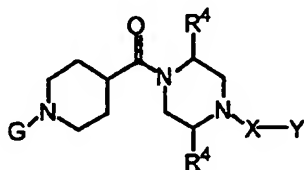
Compounds of the above formula can be prepared by coupling corresponding acid and amine precursors. The acid precursors can be prepared as shown in WO97/40024, the contents of which are incorporated herein by reference. The G-CH₂NH₂ precursors can be prepared as shown in the above-identified publication or as shown in the present application.



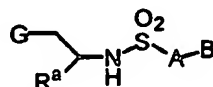
Compounds of the above formula can be prepared by coupling corresponding acid and amine precursors. The acid precursors can be prepared as shown in WO98/17274, the contents of which are incorporated herein by reference. The G-CH₂NH₂ precursors can be prepared as shown in the above-identified publication or as shown in the present application.



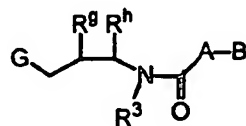
Compounds of the above formula can be prepared by coupling corresponding G-benzoic acid and piperazine precursors. The G-benzoic acid precursors can be prepared similarly to the methods shown in WO98/21188, the contents of which are incorporated herein by reference. For example, the G-benzoic acid precursors can be prepared by coupling an activated G (e.g., a metallated ring) with a leaving group-benzoic acid (e.g., halo-benzoic acid) as shown in the above-identified publication. The piperazine precursors can be prepared by coupling of the desired piperazine with the desired X-Y group, wherein X contains a leaving group, as shown in the above-identified application or in the present application.



Compounds of the above formulas can be prepared by coupling corresponding benzoic acid and piperazine precursors. The G-piperidinyl acid or G-piperazinyl acid precursors can be prepared similarly to the methods shown in WO96/10022, the contents of which are incorporated herein by reference. For example, the G-piperidinyl acid or G-piperazinyl acid precursors can be prepared by coupling a G-leaving group (e.g., G-halogen) with a piperidinyl acid or piperazinyl acid as shown in the above-identified publication. The piperidine and piperazine precursors can be prepared by coupling of the desired piperazine with the desired X-Y group, wherein X contains a leaving group, as shown in the above-identified application or in the present application.

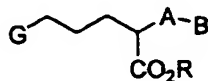


Compounds of the above formula can be prepared by coupling corresponding sulfonic acid and amine precursors. The sulfonic acid precursors can be prepared as shown in WO96/33993, the contents of which are incorporated herein by reference. The G-CH₂CH(R^a)NH₂ precursors can be prepared as shown in the above-identified publication or as shown in the present application.



Compounds of the above formula can be prepared by coupling corresponding G-CHO or G-CH₂Br and (R^g)CH₂CH₂(R^h)N(R³)C(O)-A-B precursors. The (R^g)CH₂CH₂(R^h)N(R³)C(O)-A-B precursors can be prepared as shown in WO97/24118, the contents of which are incorporated

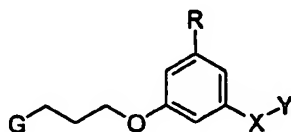
herein by reference. The G-CHO and G-CH₂Br precursors can be prepared as shown in the above-identified publication or as shown in the present application.



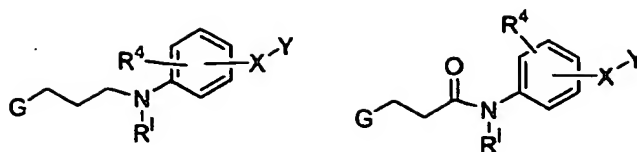
5

Compounds of the above formula can be prepared by coupling corresponding G-(CH₂)₃-leaving group and ester precursors. The ester precursors can be prepared as shown in EP/0540051, the contents of which are incorporated herein by reference. The G-(CH₂)₃-leaving group precursors can be prepared as shown in the above-identified publication or other publications described herein or as shown in the present application.

Compounds of the above formula when G contains an amine linker can be prepared by displacing a leaving group off of the remainder of the molecule with corresponding G-amine precursor. The remainder of the molecule can be prepared as shown in JP10/1467, the contents of which are incorporated herein by reference. The G-NH₂ precursors can be prepared as shown in the above-identified publications or as shown in the present application.



Compounds of the above formula can be prepared by coupling corresponding G-(CH₂)₃-leaving group and phenol precursors. The phenol precursors can be prepared as shown in WO97/36580, the contents of which are incorporated herein by reference or as shown in the present application. The G-(CH₂)₃-leaving group precursors can be prepared as shown in the above-identified publication or other publications described herein or as shown in the present application.



Compounds of the above formulas can be prepared by coupling corresponding aniline and $G-(CH_2)_3$ -leaving group or $G-(CH_2)_2CO_2H$ precursors. The aniline precursors can be prepared as shown in EP/0540051, JP10/1467, and WO96/16940, the contents of which are incorporated herein by reference. The $G-(CH_2)_3$ -leaving group or $G-(CH_2)_2CO_2H$ precursors can be prepared as shown in the above-identified publication or other publications described herein or as shown in the present application.

Many of the compounds of the present invention can be prepared from $G-NH_2$, where G represents a residue which is either the P1 residue described above, a suitably protected form of the P1 residue, or an intermediate which can be transformed at a later stage of the synthesis into the P1 residue. Scheme I describes procedures by which the amino residue of $G-NH_2$ can be transformed into a variety of different functionalities which are useful for assembling the compounds of the present invention. $G-NH_2$ I can be diazotized with sodium nitrite in the presence of aqueous sulfuric acid to produce the hydroxy derivative II. Diazotization of I in acidic media followed by treatment with copper (I) bromide affords the bromo derivative III. The bromo derivative is a very useful intermediate for further functionalization. Treatment of III with magnesium metal generates a Grignard reagent which can react with suitably protected bromoglycinate derivatives to afford amino acid derivatives IV. There are a wide variety of methods available for introducing simple carbon-atom based functionality starting with bromide III. Transmetallation with an organolithium reagent such as tert-butyllithium or

n-butyllithium is readily accomplished at low temperature. The formed organolithium species can react with a wide variety of electrophiles. For example, reaction with dimethylformamide produces the aldehyde derivative V, while

5 reaction with an alkyl chloroformate or an alkyl cyanoformate produces an ester derivative. The ester functionality can be reduced with a variety of hydride reducing agents such as lithium aluminum hydride or diisobutylaluminum hydride to afford the alcohol VI. The

10 alcohol VI can also be prepared by reduction of aldehyde V, such as with sodium borohydride. The bromide III can also react through palladium-mediated processes. For example, reaction of III with an alcohol or amine and a catalyst such as tetrakis-triphenylphosphine palladium under a carbon

15 monoxide atmosphere leads to esters G-CO₂R or amides G-CONR₂ via a carbonyl insertion reaction. A particularly useful amide G-CONR₂ available by this procedure is the N-methyl-N-methoxy amide, obtained when N-methyl-N-methoxyamine is used in the carbonyl insertion reaction. This amide is readily

20 reduced to aldehyde V with hydride reducing agents such as diisobutylaluminum hydride. The alcohol VI, readily available by a variety of methods as described above can be converted to the bromide derivative VII by many methods, such as by treatment with carbon tetrabromide and

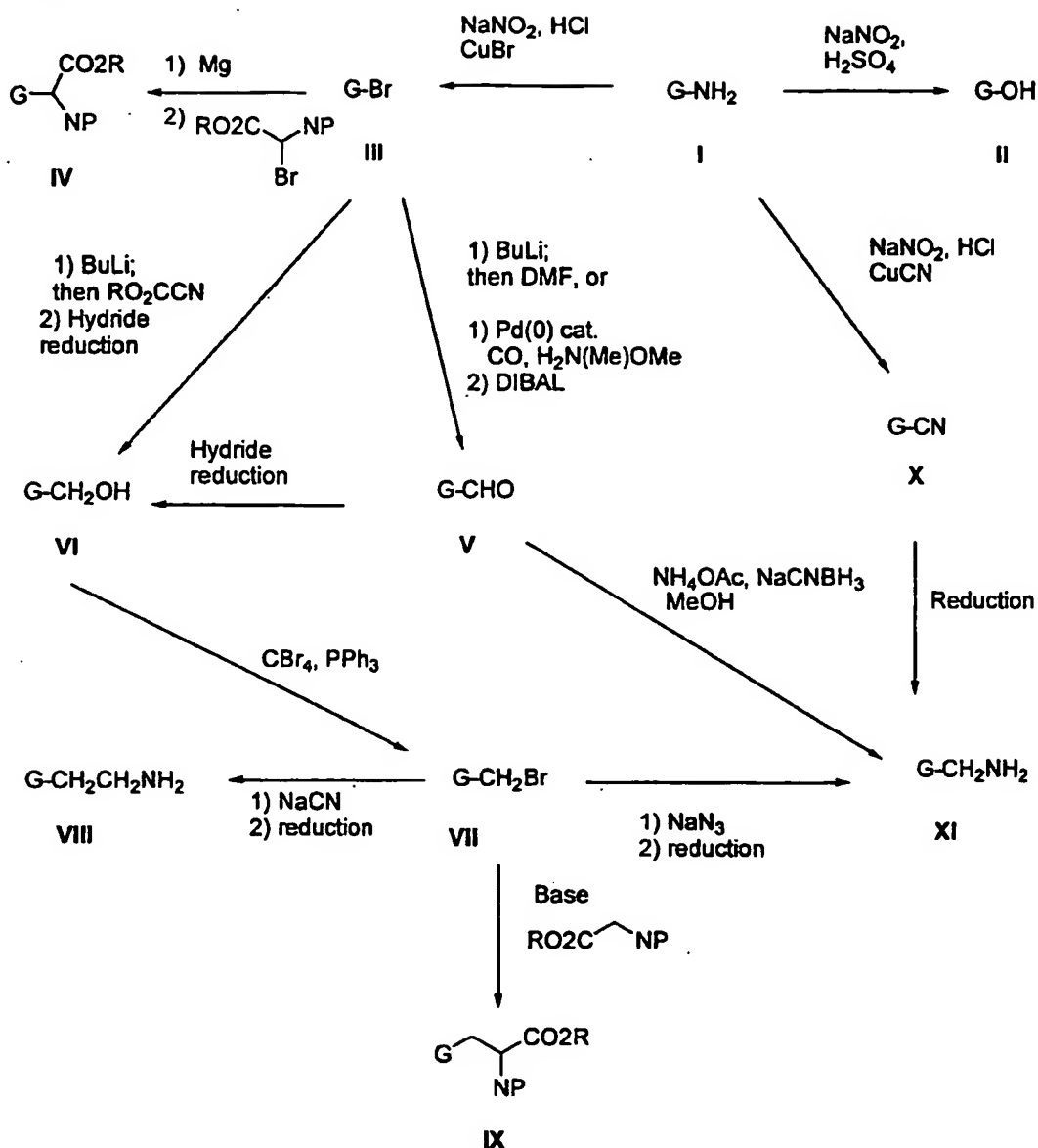
25 triphenylphosphine. Another method for the preparation of bromide VII, not shown in Scheme I, involves the radical bromination of an intermediate G-CH₃, which is readily available by methods known to those skilled in the art of organic synthesis. This radical bromination is readily

30 accomplished by treating G-CH₃ with N-bromosuccinimide in refluxing carbon tetrachloride in the presence of a radical initiator such as AIBN. The bromide VII is a particularly useful intermediate for the preparation of the compounds of the present invention. Displacement of the bromide can be

35 accomplished by treatment with sodium or potassium cyanide

in a solvent such as DMF or DMSO at room temperature or elevated temperature to give a cyano derivative. Reduction of the nitrile, such as by catalytic hydrogenation or by treatment with sodium borohydride and cobalt (II) chloride, gives the amino derivative VIII. The bromide can also be displaced by appropriate N-protected glycines, such as N-(diphenylmethylene)glycine ethyl ester, to give the amino acid derivatives IX. This reaction is accomplished by heating VII and the glycine in the presence of a base such as potassium carbonate and a quaternary ammonium salt such as tetrabutylammonium bromide in a solvent such as acetonitrile. The bromide can also be displaced with sodium azide in a solvent such as DMF or DMSO at elevated temperatures to give an azide intermediate. The azide is readily reduced by a variety of reducing agents, such as by catalytic hydrogenation or by tin (II) chloride, to afford the amino derivative XI. A variety of other methods are available for the preparation of the amino derivative XI. For example, reductive amination of aldehyde V with ammonium acetate and sodium cyanoborohydride affords XI. Alternatively, the amine G-NH₂, I can be diazotized as described above and reacted with copper (I) cyanide to afford the nitrile X. The nitrile can be reduced to form amine XI by a variety of methods, such as by catalytic hydrogenation or by reduction with sodium borohydride in the presence of cobalt (II) chloride. A variety of other methods for the preparation of the intermediates described in Scheme I are available and are known to those skilled in the art. The particular method used for the preparation of the required intermediates will depend on additional functionality present on group "G", and it will be appreciated by those skilled in the art that certain protecting group strategies may be required and that reaction conditions and the order of steps may require modification.

Scheme I



5 As an illustration, in Scheme II is shown how the chemistry in Scheme I can be applied to the preparation of intermediates in which the group G is a suitably protected 3-aminobenzisoxazole, prepared as described in Schemes XXVIII and XXXI. As described previously, the amino group of XII can be transformed into the corresponding hydroxyl,

10 cyano or bromide derivatives XIII, XXI, and XIV,

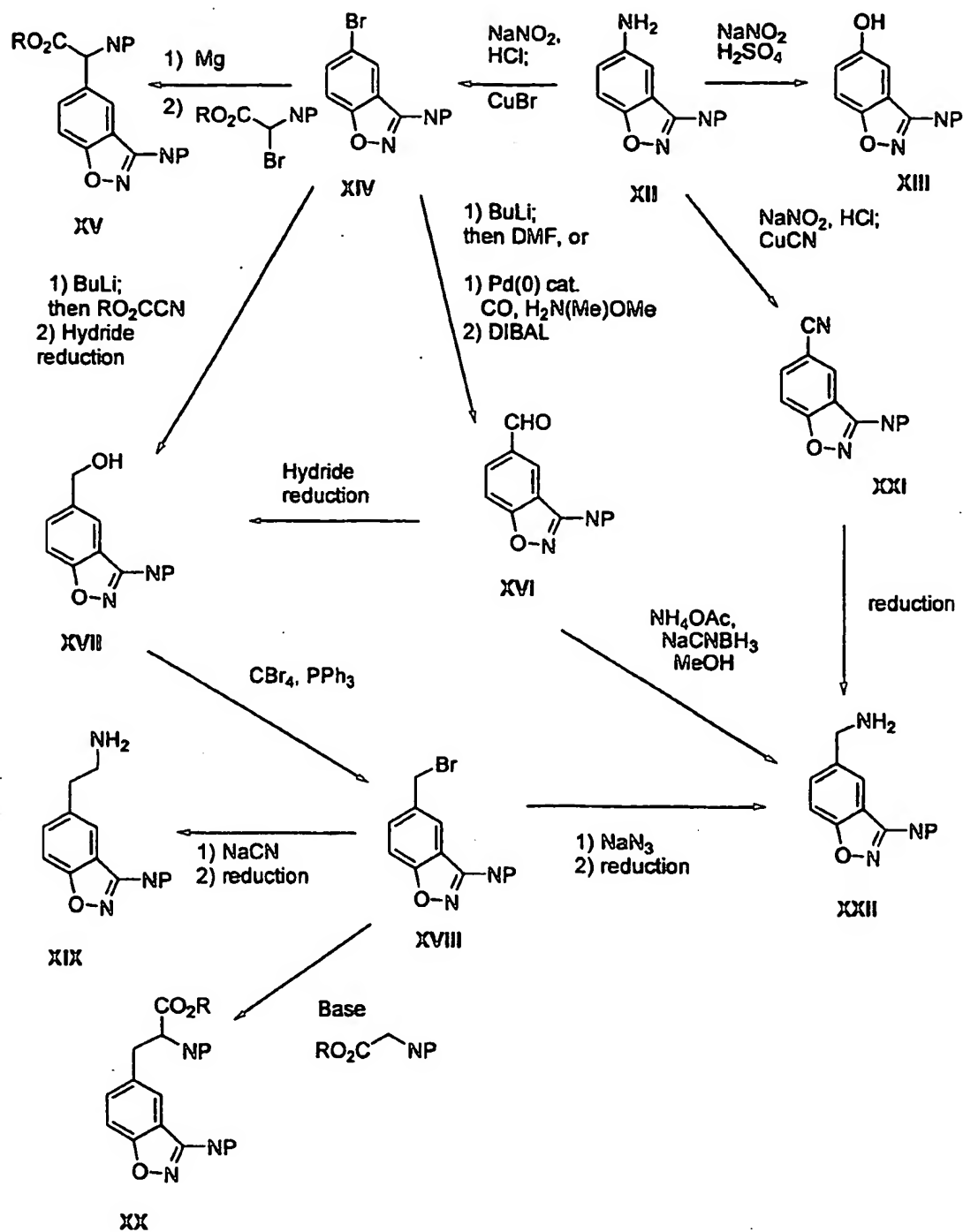
respectively, via its derived diazonium ion. The bromide is a particularly useful intermediate and can be transformed by a wide variety of anionic or palladium-mediated processes into amino acid derivatives XV, aldehydes XVI and alcohols

5 XVII, in addition to various ester and amide derivatives.

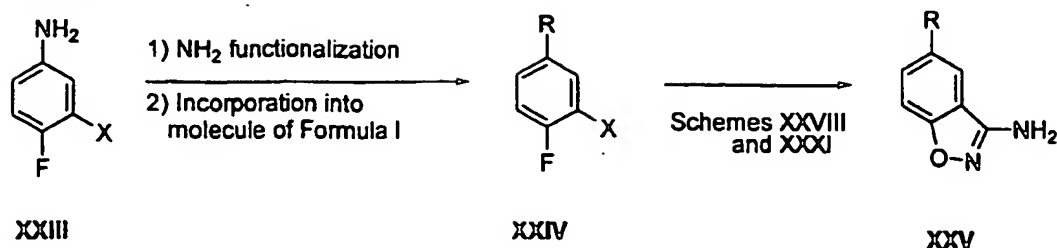
The aldehyde and alcohol derivatives are useful for the preparation of the bromide XVIII, which in turn can be transformed into a wide variety of intermediates such as amines XIX and XXII, and amino acid derivatives XX.

10 Alternatively, in the case of the 3-aminobenzisoxazole derivatives described in Scheme II, it is also possible to form the aminobenzisoxazole ring at a later stage of the synthesis, thereby carrying out the chemistry described in Scheme II on a latent form of the aminobenzisoxazole G
15 group, as shown in Scheme III. The amine XXIII corresponds to G-NH₂, where G represents an intermediate which can be transformed at a later stage of the synthesis into the P1 residue. In the aminobenzisoxazole case, X can represent cyano, which is the desired group for formation of the
20 aminobenzisoxazole ring, or X can represent a group such as Br, NH₂, NO₂, ester, amide, etc., which can easily be converted into a cyano group by a variety of methods known to those skilled in the art. The intermediate XXIII can be converted into XXIV, where R represents the remainder of the
25 inhibitor, by methods described in other schemes, and XXIV can be converted into the aminobenzisoxazole XXV as described previously.

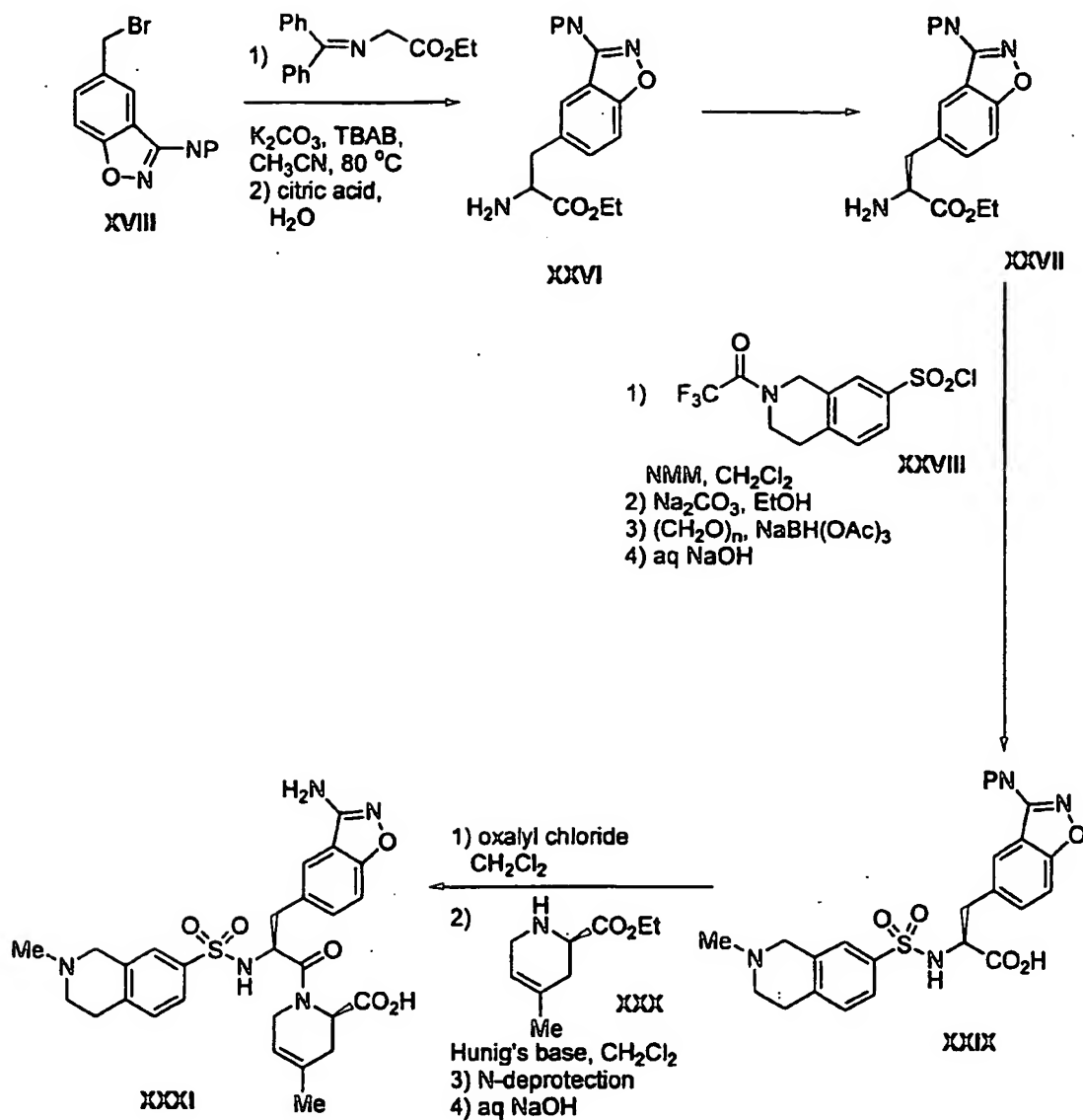
Scheme II



Scheme III

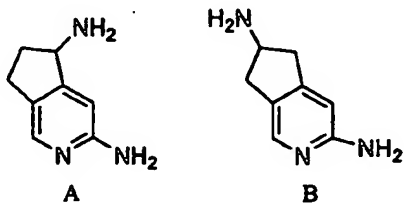


- 5 In Scheme IV is shown how the chemistry in Scheme II can be applied to a particularly preferred compound of the present invention. Alkylation of N-
- (diphenylmethylene)glycine ethyl ester with bromide XVIII using potassium carbonate as base and tetrabutylammonium
- 10 bromide in acetonitrile affords, after deprotection, aminoester XXVI. This racemic compound can be resolved, preferably by selective hydrolysis of a suitable N-protected derivative with an esterase such as α -chymotrypsin, to afford, after reesterification and N-deprotection, the
- 15 preferred (S)-aminoester XXVII. Coupling with the sulfonyl chloride XXVIII and subsequent removal of the trifluoroacetate group under basic conditions, N-methylation via reductive amination with paraformaldehyde and sodium triacetoxyborohydride, and basic ester hydrolysis affords
- 20 XXIX. Formation of the acid chloride of XXIX with oxalyl chloride is followed by addition of the tetrahydropyridine XXX to produce an amide. N-deprotection and basic ester hydrolysis yields the preferred compound XXXI.



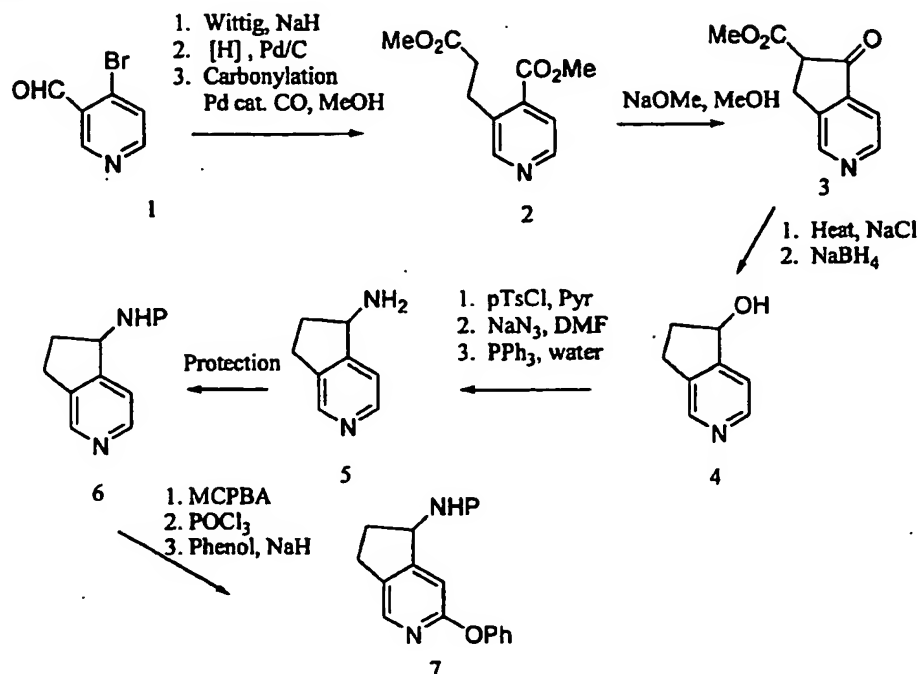
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Compounds wherein G is A or B, shown below:



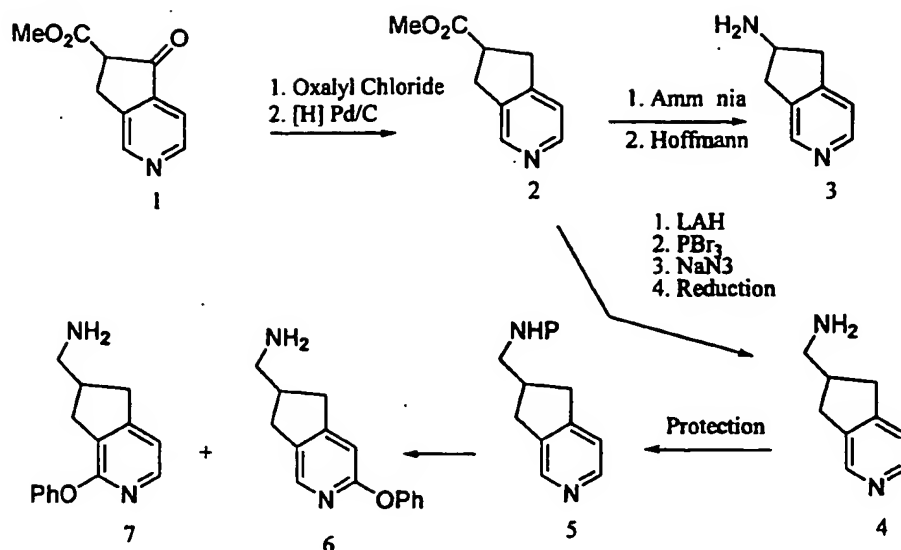
A can be prepared via the methodology outlined in Scheme V below.

Scheme V



- Removal of the amino protecting group followed by further manipulation can afford key starting materials wherein the amino is a benzylamine or alpha-amino acid or all analogs stated earlier. The starting material can also be obtained from intermediate 4 via an SN2 type displacement of the o-tosylate. Decarboxylation of intermediate 3 affords the ketone analog which also can be further manipulated to afford additional starting materials G.
- Coupling of analogs such as intermediate 7 via standard techniques followed by displacement of the phenoxy pyridine via standard techniques known to those in the art should afford the compounds of formula A. Chiral compounds can be separated via chiral HPLC techniques or by co-crystallization methods with a known chiral precursor.

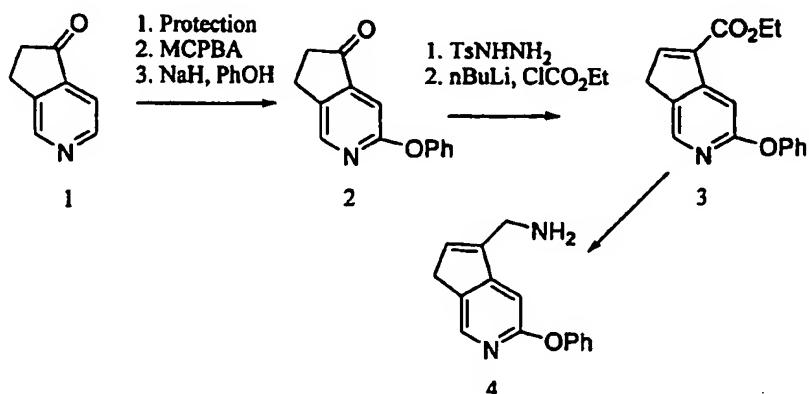
Compounds wherein G is of formula B as shown above can be prepared as shown in Scheme VI.



Via this scheme amino intermediates such as 3(B) and 5 phenoxy analogs 6 and 7 can be obtained easily via the methods previously described. These intermediates can be further coupled to requisite precursors followed by conversion of the phenoxy group to an amino via standard techniques to afford the amino-pyridyl compounds of formula 1-3.

The unsaturated analogs can be prepared according to Scheme VII.

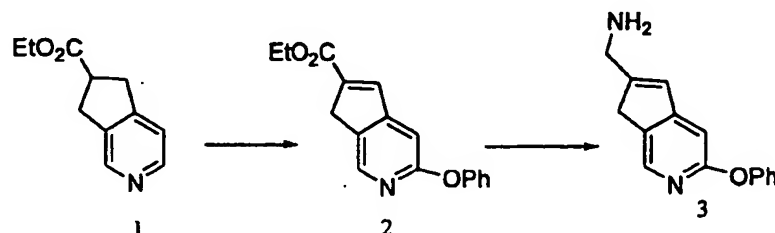
Scheme VII



Intermediate 3 can be further manipulated to afford other G intermediates via methods described previously. In a similar fashion the other unsaturated analog can be prepared via Scheme VIII shown below.

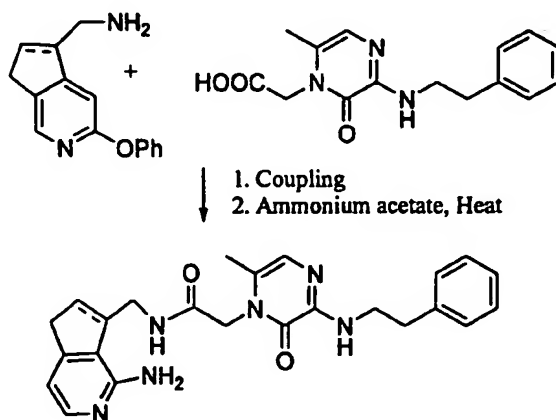
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Scheme VIII



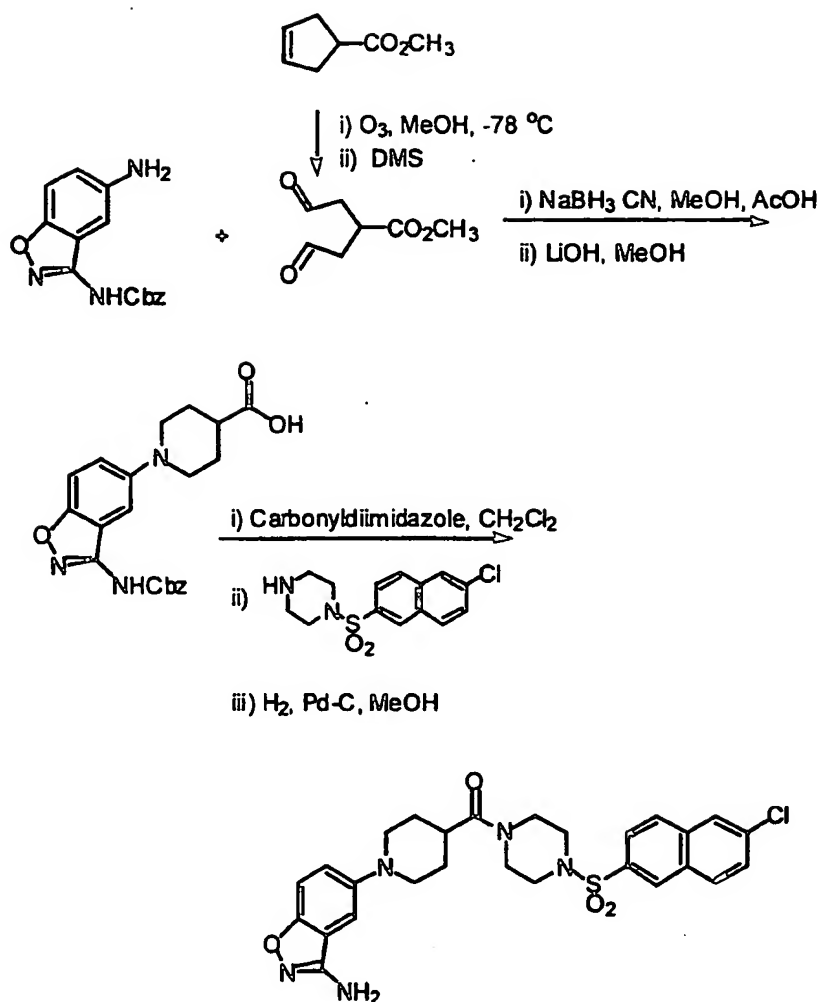
Conversion of intermediate 1-3 can be done via standard techniques known to those in the art of organic synthesis. Analog 3 can be further coupled to various intermediates to afford compounds of formula 1-3 an illustrative example is shown below in Scheme IX.

15 Scheme IX



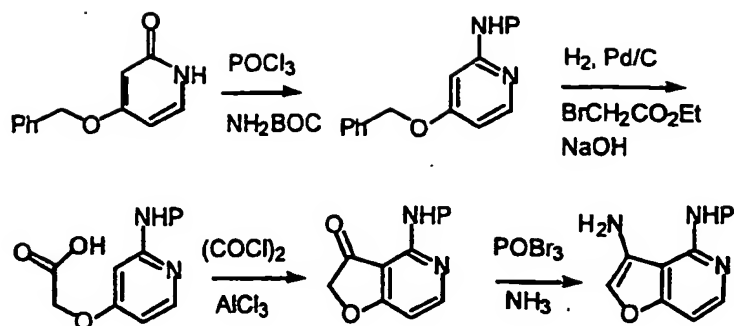
Scheme X exemplifies the preparation of compounds wherein G is 2-aminobenzisoxazole.

20



The Cbz-protected diaminobenzoisoxazole undergoes reductive
5 dialkylation with the dialdehyde prepared by the ozonolysis
of the known 3-carbomethoxy cyclopentene followed by
hydrolysis of the ester to the N-aryl isonipecotic acid.
Activation of the carboxylic acid group by treatment with
carbonyldiimidazole followed by quenching with
10 piperazine((6-chloro)naphth-2-yl)sulfonamide and removal of
the Cbz protecting group gives the target compound.

Scheme XI describes the preparation of 3-
aminobenzofuran intermediates.

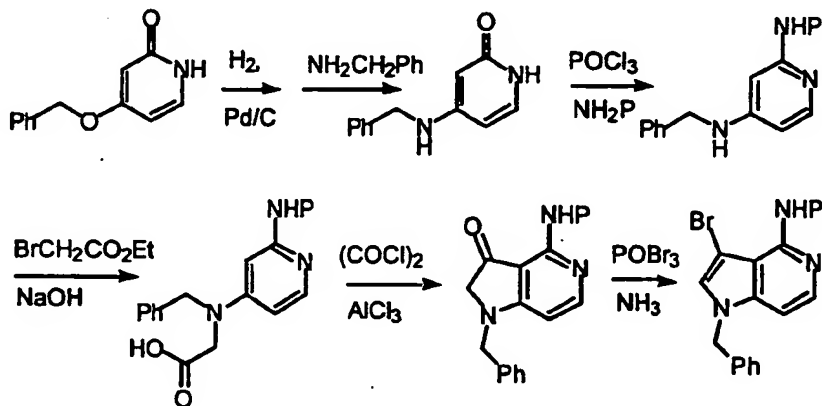


4-benzyloxy-2(1H)-pyridone (available from Aldrich) can
5 be converted to the aminopyridine derivative using standard
procedures known to the practitioners of the art.
Debenzylation, coupling with bromoethylacetate, followed by
basic hydrolysis affords an intermediate that undergoes the
Friedel-Crafts acylation.

10

Scheme XII describes the preparation of indole
intermediates.

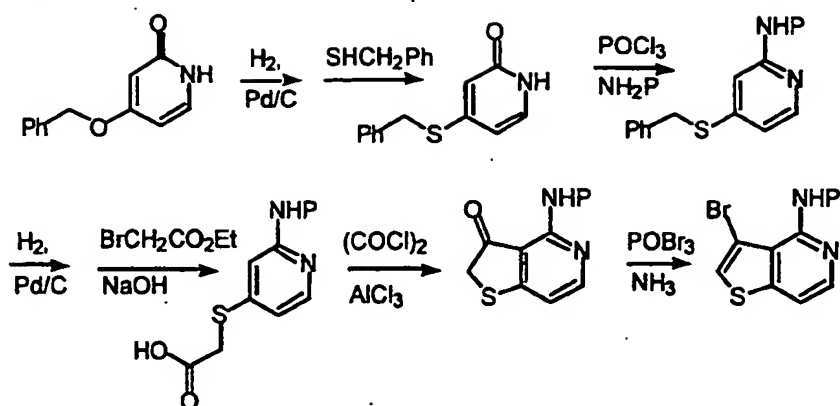
Scheme XII



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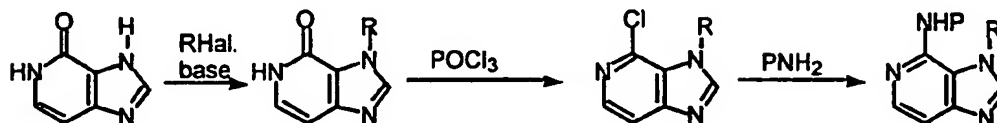
Scheme XIII describes the preparation of 3-halo-4-
aminobenzothiophene intermediates.

Scheme XIII



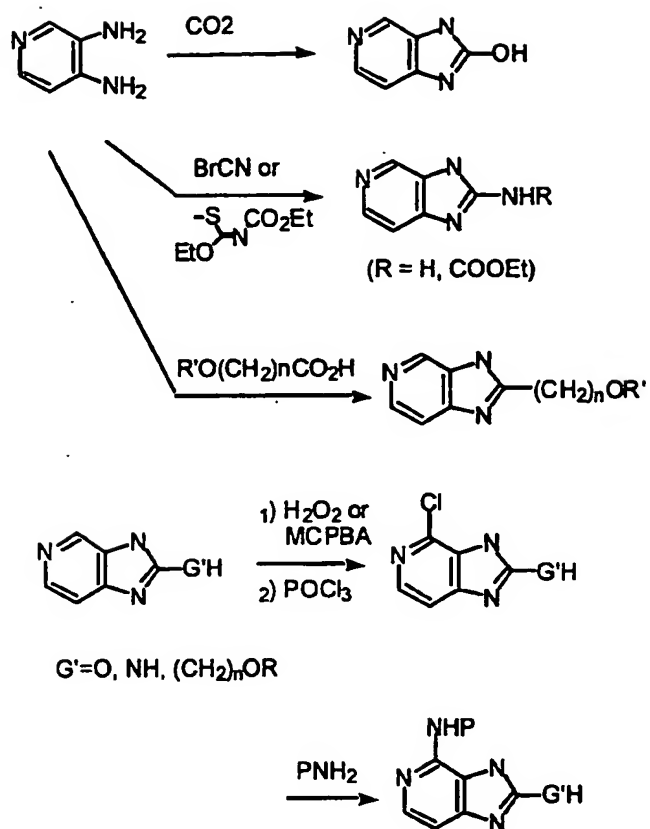
Scheme XIV describes the preparation of 1-substituted-
5 7-amino-azabenzimidazole intermediates.

Scheme XIV

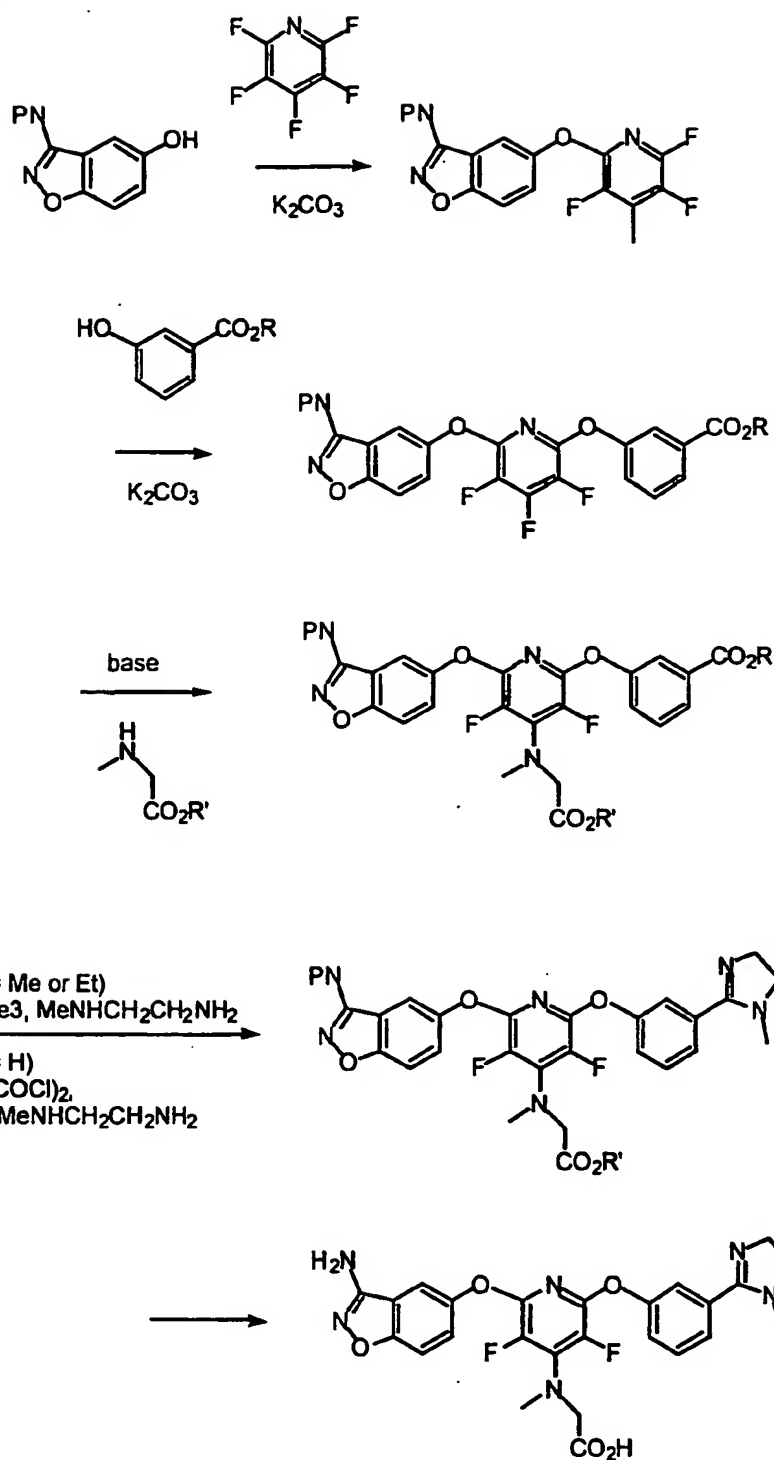


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Scheme XV describes the preparation of 2-substituted-7-
amino-azabenzimidazole intermediates.

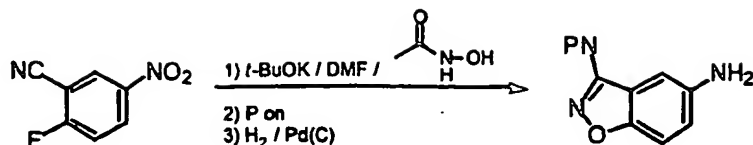


Scheme XVI describes the preparation compounds wherein
5 G is a 3-amino-5-benzisoxazoline.



Scheme XVII describes the preparation of 5-aminobenzisoxazole intermediates.

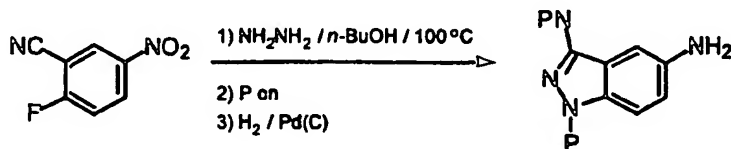
Scheme XVII



5 Synthesis of 5-aminobenzisoxazoles in which the 3-
 position may be a protected amine could be accomplished
 starting from the commercially available 3-cyano-4-
 fluoronitrobenzene. Displacement of fluorine with
 acetoxyhydroxamic acid under basic conditions followed by ring
 10 closure by subsequent addition to the nitrile would yield
 the benzisoxazole core. Suitable protection and reduction
 of the aryl nitro group would provide the desired compound.

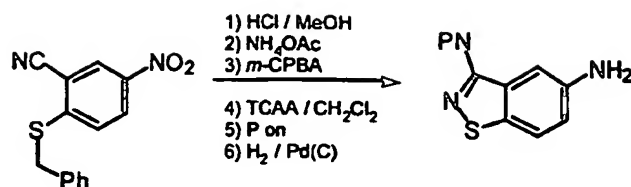
 Scheme XVIII describes the preparation of 5-
 15 aminoindazole intermediates.

Scheme XVIII



20 Synthesis of 5-aminoindazoles in which the 3-position
 may be a protected amine could be accomplished starting from
 the commercially available 3-cyano-4-fluoronitrobenzene.
 Displacement of fluorine with hydrazine followed by ring
 25 closure by subsequent addition to the nitrile would yield
 the indazole core. Suitable protection and reduction of the
 aryl nitro group would provide the desired compound.

 Scheme XIX describes the preparation of 5-
 30 aminobenzisothiazole intermediates.

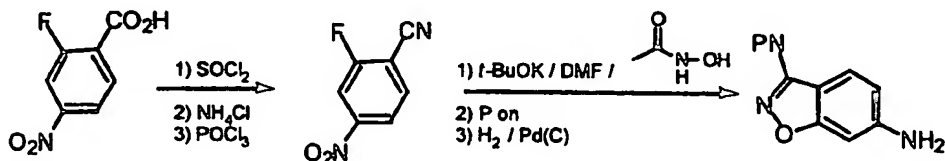


Synthesis of 5-aminobenzisothiazoles in which the 3-
5 position may be a protected amine could be accomplished
starting from the commercially available 2-benzylthio-5-
nitrobenzonitrile. Conversion of the aryl nitrile to
benzamidine, sulfoxide formation and ring
closure/debenzylation would yield the benzisothiazole core.
10 Suitable protection and reduction of the aryl nitro group
would provide the desired compound.

Scheme XX describes the preparation of 6-
aminobenzisoxazole intermediates.

15

Scheme XX



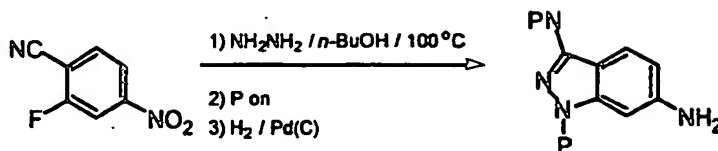
Synthesis of 6-aminobenzisoxazoles in which the 3-
20 position may be a protected amine could be accomplished
starting from commercially available 2-fluoro-4-nitrobenzoic
acid. Conversion of carboxylic acid to nitrile via standard
manipulations would give 2-fluoro-4-nitrobenzonitrile.
25 Displacement of fluorine with acetohydroxamic acid under
basic conditions followed by ring closure by subsequent
addition to the nitrile would yield the benzisoxazole core.
Suitable protection and reduction of the aryl nitro group
would provide the desired compound.

30

Scheme XXI describes the preparation of 5-aminoindazole intermediates.

Scheme XXI

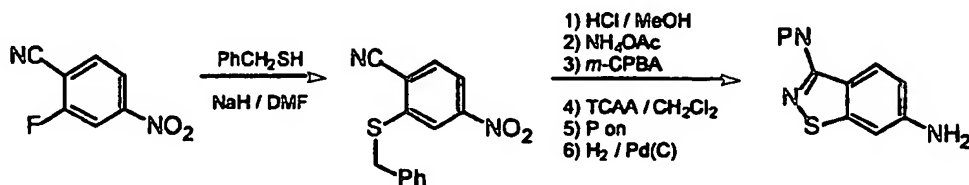
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Synthesis of 5-aminoindazoles in which the 3-position may be a protected amine could be accomplished starting from
 10 from 2-fluoro-4-nitrobenzonitrile whose synthesis is described elsewhere in this patent. Displacement of fluorine with hydrazine followed by ring closure by subsequent addition to the nitrile would yield the indazole core. Suitable protection and reduction of the aryl nitro
 15 group would provide the desired compound.

Scheme XXII describes the preparation of 6-aminobenzisothiazole intermediates.

20 Scheme XXII

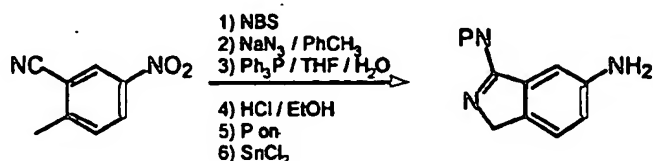


Synthesis of 6-aminobenzisothiazoles in which the 3-position may be a protected amine could be accomplished
 25 starting from 2-fluoro-4-nitrobenzonitrile whose synthesis is described elsewhere in this patent. Displacement of fluorine with benzylthio anion yields 2-benzylthio-4-nitrobenzonitrile. Conversion of the aryl nitrile to benzamidine, sulfoxide formation and ring
 30 closure/debenzylation would yield the benzisothiazole core.

Suitable protection and reduction of the aryl nitro group would provide the desired compound.

Scheme XXIII describes the preparation of 6-aminoisoindole intermediates.

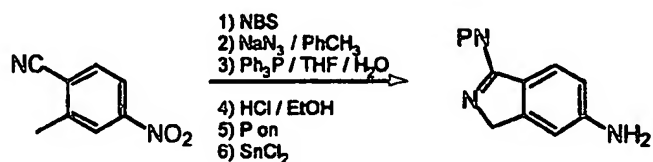
Scheme XXIII



Synthesis of 6-aminoisoindoles in which the 1-position may be a protected amine could be accomplished starting from commercially available 2-cyano-4-nitrotoluene. Bromination of tolyl methyl to give a benzyl bromide followed by displacement with azide and reduction to benzylamine would cyclize to the isoindole core. Suitable protection and reduction of the aryl nitro group would provide the desired compound.

Scheme XXIV describes the preparation of 5-aminoisoindole intermediates.

Scheme XXIV

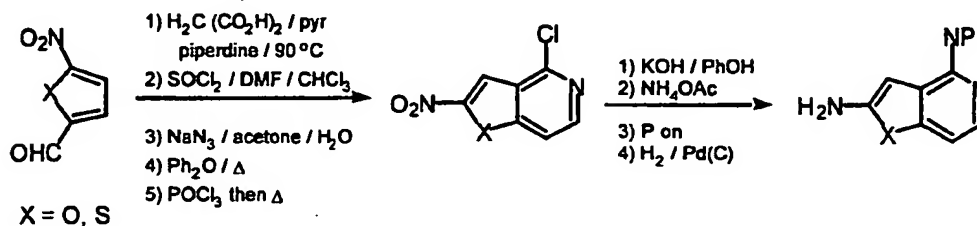


Synthesis of 5-aminoisoindoles in which the 1-position may be a protected amine could be accomplished starting from commercially available 2-cyano-5-nitrotoluene. Bromination of tolyl methyl to give a benzyl bromide followed by displacement with azide and reduction to benzylamine would cyclize to the isoindole core. Suitable protection and

reduction of the aryl nitro group would provide the desired compound.

Scheme XXV describes the preparation of 2-aminoindole derivatives a intermediates.

Scheme XXV

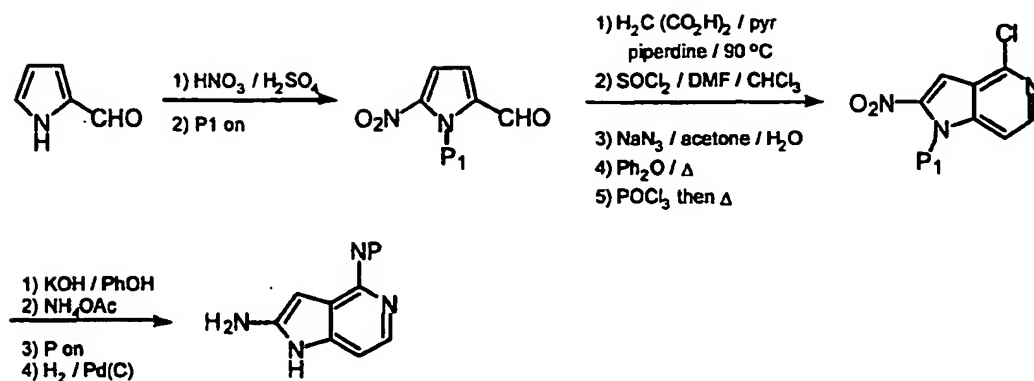


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Synthesis of the desired compounds in which the 4-position may be a protected amine could be accomplished starting from the commercially available furan or thiophene. Using literature methods (*J. Med. Chem.* 1989, 32, 1147) one could obtain the 2-nitro-4-chloro-furo or thieno[3,2-c]pyridine. Displacement of the 4-chloro with phenoxide then conversion to 4-amino followed by suitable protection and reduction of the aryl nitro group would provide the desired compound.

20

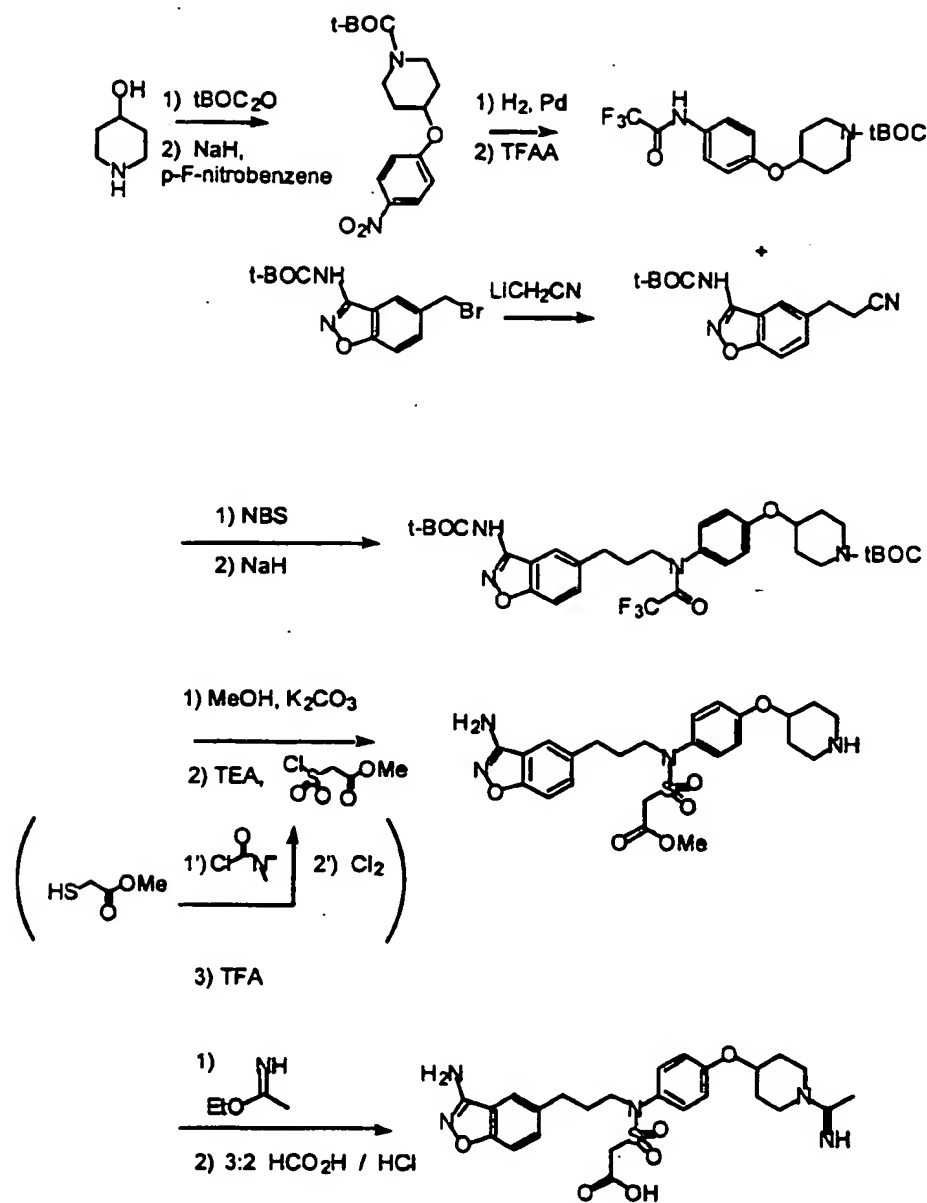
Scheme XXVI describes the preparation of 2-amino-1-H - pyrrolo[3,2-c]pyridine intermediates.



Synthesis of 2-amino-1-H -pyrrolo[3,2-c]pyridine in
5 which the 4-position may be a protected amine could be
accomplished starting from the commercially available
pyrrole-2-carboxaldehyde. Nitration and protection of
pyrrole nitrogen with P1 would afford the nitro/aldehyde
intermediate. Using literature methods (*J. Med. Chem.* **1989**,
10 **32**, 1147) one could obtain the 2-nitro-4-chloro-pyrrolo[3,2-
c]pyridine. Displacement of the 4-chloro with phenoxide
then conversion to 4-amino followed by suitable protection
and reduction of the aryl nitro group would provide the
desired compound.

15

Scheme XXVII describes the preparation compounds
wherein G is a 3-amino-5-benzisoxazoliny propyl group.



BOC-Protected aminobenzisoxazolemethylbromide can be
5 reacted with the lithium salt of acetonitrile to give the
nitrile. The nitrile can be further reacted in a similar
fashion as in WO96/16940 to give the desired compound.

The A-B moieties of the present can be prepared by
methods known to those of skill in the art. For example,
10 preparation of the "A-B" of the present invention moieties
can follow the same methods described in WO97/23212,

WO97/30971, WO97/38984, WO98/01428, WO98/06694, WO98/28269, WO98/28282, WO98/57934, WO98/57937, and WO98/57951, the contents of which are incorporated herein by reference.

5

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa, thrombin, or both.

The effectiveness of compounds of the present invention as inhibitors of factor Xa can be determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) can be measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which can be monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i .

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m , for substrate hydrolysis can be determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research

Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship can be used to calculate K_i values:

$$(v_o - v_s) / v_s = I / (K_i (1 + S / K_m))$$

where:

- v_o is the velocity of the control in the absence of inhibitor;
- v_s is the velocity in the presence of inhibitor;
- I is the concentration of inhibitor;
- K_i is the dissociation constant of the enzyme:inhibitor complex;
- S is the concentration of substrate;
- K_m is the Michaelis constant.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq 10 \mu\text{M}$. Preferred compounds of the present invention have K_i 's of $\leq 1 \mu\text{M}$. More preferred compounds of the present invention have K_i 's of $\leq 0.1 \mu\text{M}$. Even more preferred compounds of the present invention have K_i 's of $\leq 0.01 \mu\text{M}$. Still more preferred compounds of the present invention have K_i 's of $\leq 0.001 \mu\text{M}$.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes,

the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is
5 determined for each treatment group. The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) may also be useful as inhibitors of serine proteases, notably human thrombin,
10 plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility
15 as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Compounds of the present invention can be shown to be
20 direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* 265, 18289-18297 (1990),
25 herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) can be monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is
30 indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, can be incubated with various substrate concentrations ranging from 0.20 to
35 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity can be assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate

hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk.

5 Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq 10 \mu\text{M}$. Preferred compounds of the present invention have K_i 's of $\leq 1 \mu\text{M}$. More preferred compounds of the present invention have K_i 's of $\leq 0.1 \mu\text{M}$. Even more preferred compounds of the present
10 invention have K_i 's of $\leq 0.01 \mu\text{M}$. Still more preferred compounds of the present invention have K_i 's of $\leq 0.001 \mu\text{M}$.

 The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-
15 coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

 The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically
20 effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

25 By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the
30 same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in
35 combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors

such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicylic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A₂-receptor antagonists and thromboxane-A₂-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boro peptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boro peptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α -aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiuronium

analogues thereof. The term hirudin, as used herein, includes suitable derivatives or analogues of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boro-peptide thrombin inhibitors include compounds described in Kettner et al., U.S. 5,187,157 and EP 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boro-peptide thrombin inhibitors include those disclosed in WO92/07869 and EP 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an

unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function

of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

5 By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20
10 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three,
15 or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal
20 delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or
25 carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

30 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium
35 sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water,

and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will

ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams

of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

5 A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

10 Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline 15 cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

20 A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

25 An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

30 Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage 35 form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material

which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients.

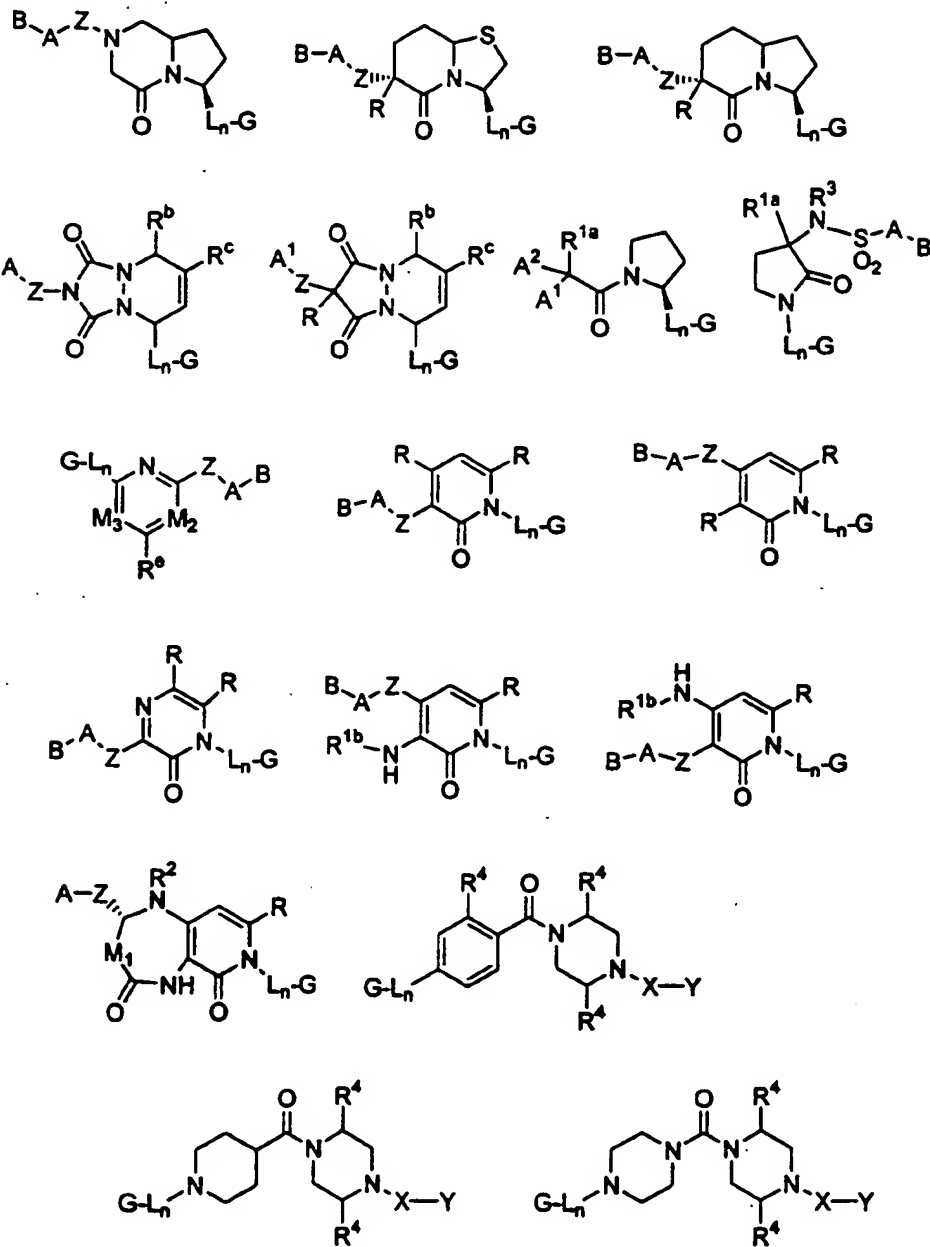
Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

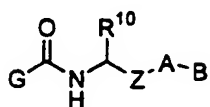
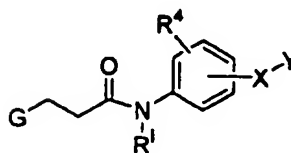
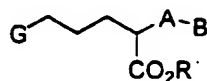
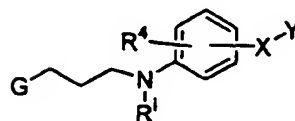
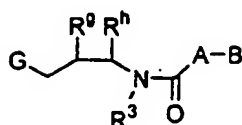
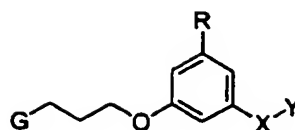
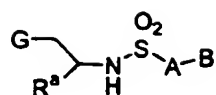
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound selected from the group:

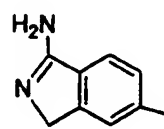
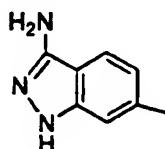
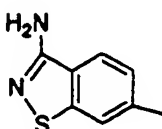
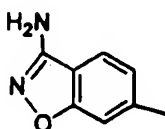
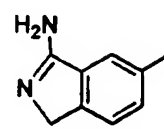
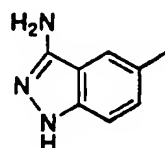
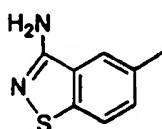
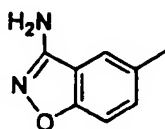


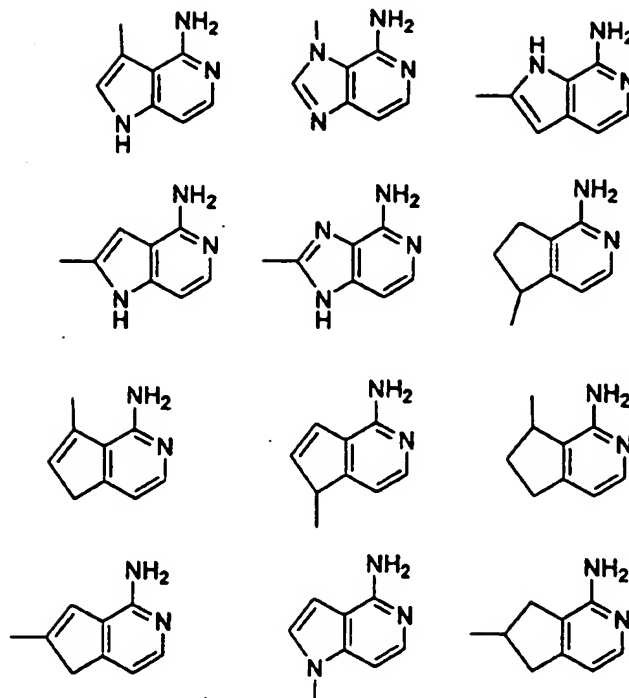


or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

5

G is selected from the group:





L_n is a linker which is absent or is selected from O, S, CH_2 ,

$*CH_2NHC(O)$, $*CH(R^a)NHC(O)$, $*CH_2NHC(O)CH_2$, and

5 $*CH(R^a)NHC(O)CH_2$, provided that L_n and M do not form an O-N or S-N bond and the * indicates where L_n is bonded to G;

M^1 is absent or is CHR;

10

M^2 is N or CR^f ;

M^3 is N or CR^d ;

15 provided that only one of M^2 and M^3 is N;

R^a is selected from $C(O)C(O)OR^3$, $C(O)C(O)NR^2R^{2a}$, and $C(O)-A$;

R^b is selected from H, R, phenyl, C_{1-10} alkyl, and C_{2-5}
20 alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

5

R^d is selected from H, F, and Cl;

R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered

aromatic heterocyclic system containing from 1-4

10 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1b}R^3)-$
 NR^3- or $-N=CR^2-NR^3-$;

15

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1b}R^3)-C(O)-$
 NR^3- or $-NR^3-CR^2=N-$;

20

R^g is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl,
 $C(O)NH_2$, and NH_2 ;

R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -
 25 phenyl;

R^i is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and
 $C(O)OR^3$;

30 R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl,
 benzyl, OCF_3 , CF_3 , $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

Z is selected from a $(CR^8R^9)_{1-4}$, $(CR^8R^9)_rO(CR^8R^9)_r$,
 $(CR^8R^9)_rNR^3(CR^8R^9)_r$, $(CR^8R^9)_rC(O)(CR^8R^9)_r$,

- $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{OC}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$,
5 $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_p(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_2(\text{CH}=\text{CH})$,
 $(\text{CCR}^8\text{R}^9)_r\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2(\text{CR}^8\text{R}^9)_r$, and
 $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, provided that Z does not form
a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with the
groups to which Z is attached;
- 10 R^{1a} is absent or selected from $-(\text{CH}_2)_r\text{-R}^{1'}$, $-\text{CH}=\text{CH-R}^{1'}$,
 $\text{NHCH}_2\text{R}^{1''}$, $\text{OCH}_2\text{R}^{1''}$, $\text{SCH}_2\text{R}^{1''}$, $\text{NH}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$,
 $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$;
- 15 $\text{R}^{1'}$ is selected from H, C₁₋₃ alkyl, F, Cl, Br, I, -CN, -CHO,
 $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OR}^2$, NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $\text{OC}(\text{O})\text{R}^2$,
 $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$, $\text{S}(\text{O})_p(\text{CH}_2)_r\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$,
 $\text{C}(=\text{NR}^{2c})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$,
 $\text{OC}(\text{O})\text{NR}^{2a}\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$,
20 $\text{NR}^2\text{SO}_2\text{R}^{2b}$, C₃₋₆ carbocyclic residue substituted with 0-2
R⁴, and 5-10 membered heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R⁴;
- 25 $\text{R}^{1''}$ is selected from H, $\text{CH}(\text{CH}_2\text{OR}^2)_2$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
 $\text{S}(\text{O})\text{R}^{2b}$, $\text{S}(\text{O})_2\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;
- R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted
with A;
- 30 R^2 , at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl,
benzyl, C₃₋₆ carbocyclic residue substituted with 0-2

R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

5 R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ cycloalkylmethyl substituted with 0-2 R^{4b}, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O,
10 and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system
15 containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue
20 substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

25 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group
30 consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

5 R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and phenyl;

10 A is selected from:

C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

15

A¹ is H or A;

alternatively, A and A¹ and the carbon to which they are attached combine to form fluorene;

20

A² is selected from H, A, and CHA³A⁴;

A³ is selected from H, A, C₁₋₄ alkyl, and -(CH₂)_pNR²R^{2a};

25 A⁴ is H or A;

B is selected from: H, Y, and X-Y

30 X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -CR²(NR^{1''}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -OS(O)₂-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, 35 -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-,

-NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and
-OCR²R^{2a}-;

Y is selected from:

- 5 (CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N,
or S-N bond,
C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
5-10 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O, and
10 S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

- R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
15 Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a},
C(=NR²)NR²R^{2a}, C(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a},
C(O)NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄
alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, NHCH₂R^{1''}, OCH₂R^{1''},
20 SCH₂R^{1''}, N(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and
S(CH₂)₂(CH₂)_tR^{1'};

- alternatively, one R⁴ is a 5-6 membered aromatic heterocycle
containing from 1-4 heteroatoms selected from the group
25 consisting of N, O, and S;

- R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
(CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, Cl, Br, F, I, C₁₋₄ alkyl,
-CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b},
30 C(O)NR²R^{2a}, C(O)NH(CH₂)₂NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)R^{3c},
C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a},
NR²SO₂-C₁₋₄ alkyl, C(O)NHSO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
S(O)_pR⁵, and (CF₂)_rCF₃;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R⁵;

5

R^{4b}, at each occurrence, is selected from H, =O, (CH₂)_rOR³, F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR³R^{3a}, (CH₂)_rC(O)R³, (CH₂)_rC(O)OR^{3c}, NR³C(O)R^{3a}, C(O)NR³R^{3a}, NR³C(O)NR³R^{3a}, C(=NR³)NR³R^{3a}, NR³C(=NR³)NR³R^{3a}, SO₂NR³R^{3a}, NR³SO₂NR³R^{3a}, NR³SO₂-C₁₋₄ alkyl, NR³SO₂CF₃, NR³SO₂-phenyl, S(O)_pCF₃, S(O)_p-C₁₋₄ alkyl, S(O)_p-phenyl, and (CF₂)_rCF₃;

10

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl substituted with 0-2 R⁶, and benzyl substituted with 0-2 R⁶;

15

R⁶, at each occurrence, is selected from H, OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b}, NR²C(O)R^{2b}, NR²C(O)NR²R^{2a}, C(=NH)NH₂, NHC(=NH)NH₂, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, and NR²SO₂C₁₋₄ alkyl;

20

R⁷, at each occurrence, is selected from H, OH, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₄ alkoxycarbonyl, (CH₂)_n-phenyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxycarbonyl, C₆₋₁₀ arylmethylcarbonyl, C₁₋₄ alkylcarbonyloxy C₁₋₄ alkoxycarbonyl, C₆₋₁₀ arylcarbonyloxy C₁₋₄ alkoxycarbonyl, C₁₋₆ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C₁₋₄ alkoxycarbonyl;

25

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;

30

alternatively, R⁷ and R⁸ combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

5

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;

10 R¹⁰ is selected from H, phenyl substituted with 0-2 R^{4a}, and naphthyl substituted with 0-2 R^{4a};

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

15

p, at each occurrence, is selected from 0, 1, and 2;

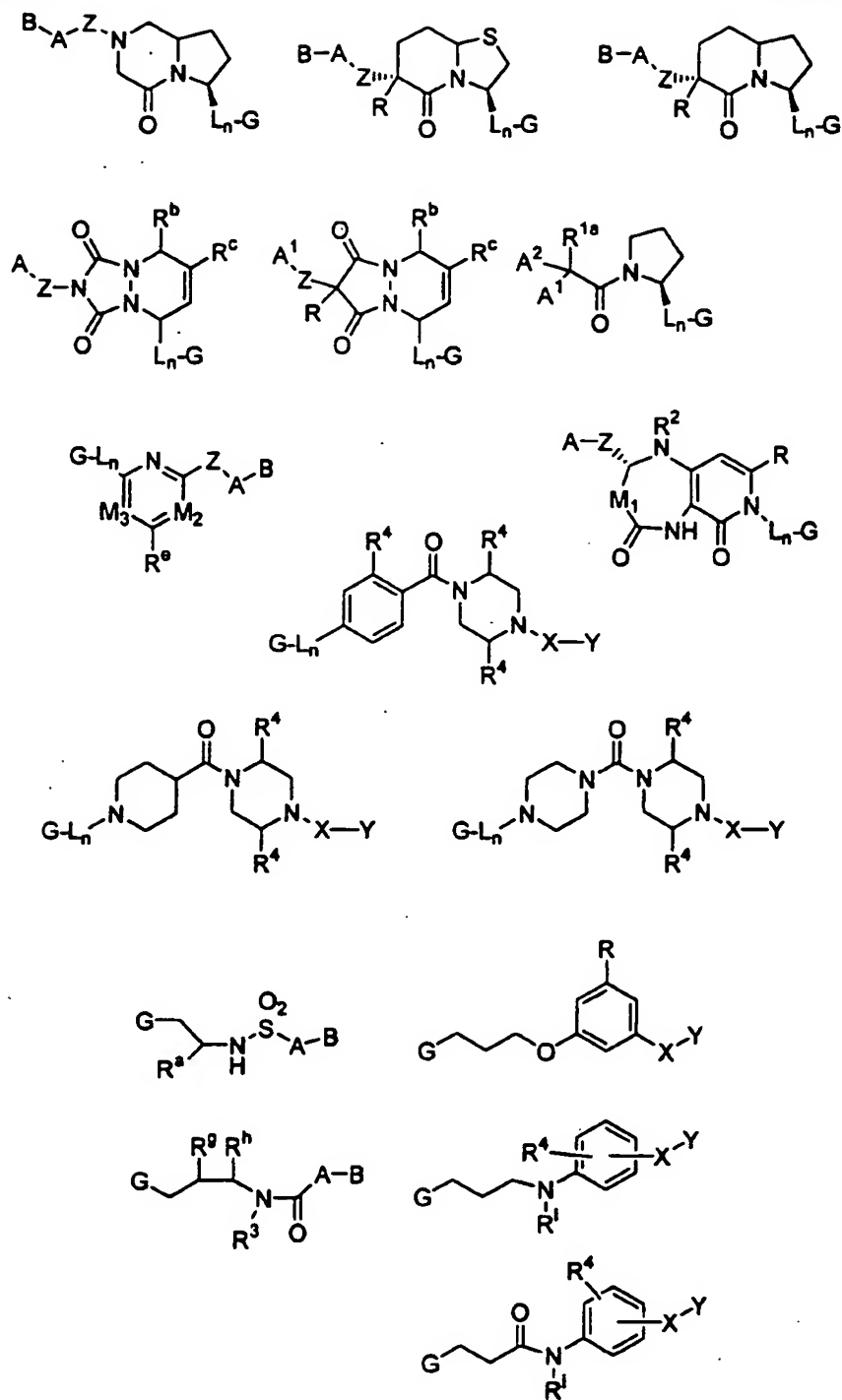
r, at each occurrence, is selected from 0, 1, 2, and 3;

20 s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

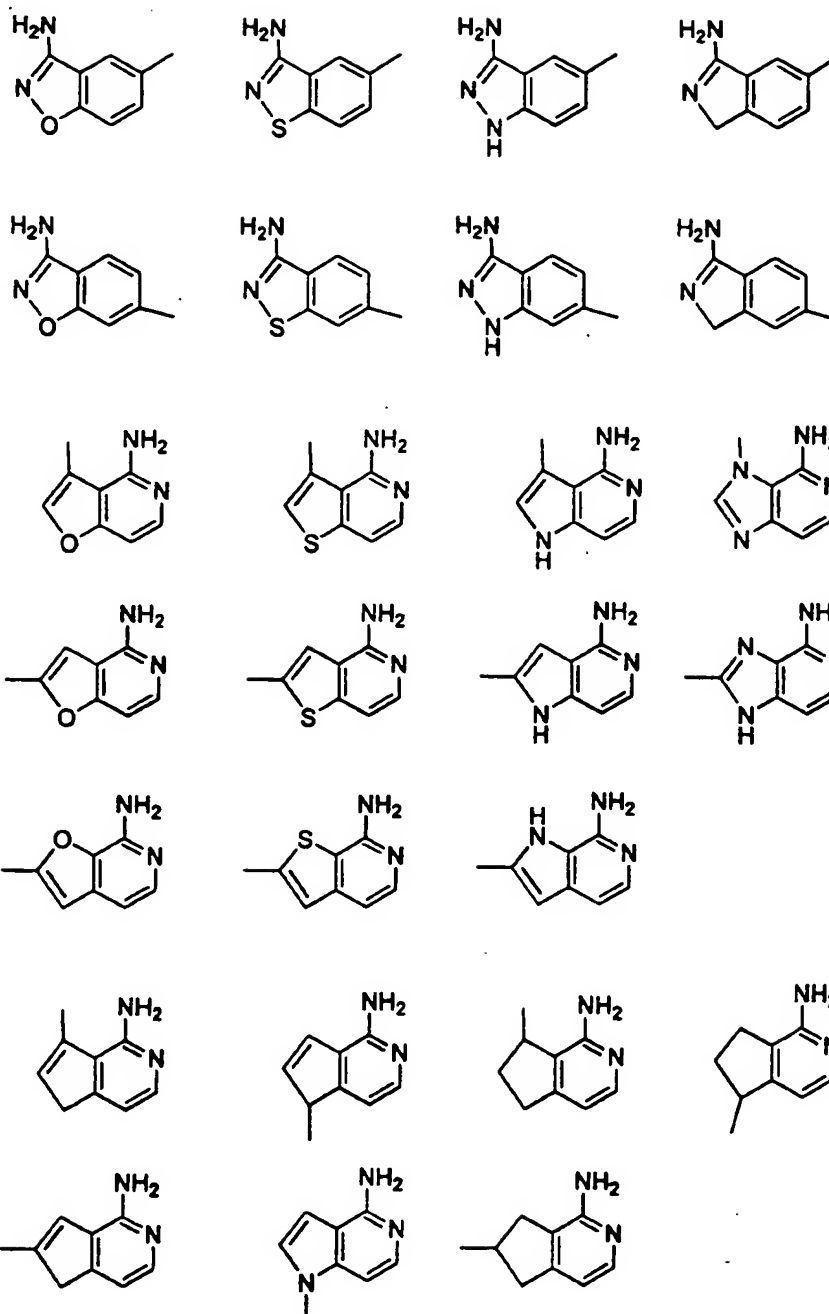
25

2. A compound selected from the group:



5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from the group:



5

L_n is a linker which is absent or is selected from O, S, CH_2 ,

$*CH_2NHC(O)$, $*CH(R^a)NHC(O)$, $*CH_2NHC(O)CH_2$, and

10 $*CH(R^a)NHC(O)CH_2$, provided that L_n and M do not form an

O-N or S-N bond and the * indicates where L_n is bonded to G;

M^1 is absent or is CHR;

5

M^2 is N or CR^f ;

M^3 is N or CR^d ;

10 provided that only one of M^2 and M^3 is N;

R^a is selected from $C(O)C(O)OR^3$, $C(O)C(O)NR^2R^{2a}$, and $C(O)-A$;

R^b is selected from H, R, phenyl, C_{1-10} alkyl, and C_{2-5}
15 alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

20

R^d is selected from H, F, and Cl;

R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered
aromatic heterocyclic system containing from 1-4
25 heteroatoms selected from the group consisting of N, O,
and S substituted with 0-2 R^4);

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1b}R^3)-$
 NR^3- or $-N=CR^2-NR^3-$;

30

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1b}R^3)-C(O)-$
 NR^3- or $-NR^3-CR^2=N-$;

35

R^g is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

5 R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

R^i is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and $C(O)OR^3$;

10 R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, benzyl, OCF_3 , CF_3 , $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

Z is selected from a $(CR^8R^9)_{1-4}$, $(CR^8R^9)_xO(CR^8R^9)_x$, $(CR^8R^9)_xNR^3(CR^8R^9)_x$, $(CR^8R^9)_xC(O)(CR^8R^9)_x$, $(CR^8R^9)_xC(O)O(CR^8R^9)_x$, $(CR^8R^9)_xOC(O)(CR^8R^9)_x$, $(CR^8R^9)_xC(O)NR^3(CR^8R^9)_x$, $(CR^8R^9)_xNR^3C(O)(CR^8R^9)_x$, $(CR^8R^9)_xOC(O)O(CR^8R^9)_x$, $(CH_2)_xOC(O)NR^3(CR^8R^9)_x$, $(CR^8R^9)_xNR^3C(O)O(CR^8R^9)_x$, $(CH_2)_xNR^3C(O)NR^3(CR^8R^9)_x$, $(CR^8R^9)_xS(O)_p(CR^8R^9)_x$, $(CR^8R^9)_xS(O)_2(CH=CH)$, $(CCR^8R^9)_xSO_2NR^3(CR^8R^9)_x$, $(CR^8R^9)_xNR^3SO_2(CR^8R^9)_x$, and $(CR^8R^9)_xNR^3SO_2NR^3(CR^8R^9)_x$, provided that Z does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with the groups to which Z is attached;

25 R^{1a} is absent or selected from $-(CH_2)_x-R^{1'}$, $-CH=CH-R^{1'}$, $NHCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $NH(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

30 $R^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_xCF_3$, $(CH_2)_xOR^2$, NR^2R^{2a} , $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_xCO_2R^{2c}$, $S(O)_p(CH_2)_xR^{2b}$, $NR^2(CH_2)_xOR^2$,

C(=NR^{2c})NR²R^{2a}, NR²C(O)R^{2b}, NR²C(O)NHR^{2b}, NR²C(O)₂R^{2a},
OC(O)NR^{2a}R^{2b}, C(O)NR²R^{2a}, C(O)NR²(CH₂)_rOR², SO₂NR²R^{2a},
NR²SO₂R^{2b}, C₃₋₆ carbocyclic residue substituted with 0-2
R⁴, and 5-10 membered heterocyclic system containing
5 from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R⁴;

R^{1''} is selected from H, CH(CH₂OR²)₂, C(O)R^{2c}, C(O)NR²R^{2a},
S(O)R^{2b}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

10 R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted
with A;

R², at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl,
15 benzyl, C₃₋₆ carbocyclic residue substituted with 0-2
R^{4b}, and 5-6 membered heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R^{4b};

20 R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl,
benzyl, C₃₋₆ cycloalkylmethyl substituted with 0-2 R^{4b},
C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and
5-6 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O,
25 and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy,
C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted
with 0-2 R^{4b}, and 5-6 membered heterocyclic system
30 containing from 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-2 R^{4b};

5 R^{2c} , at each occurrence, is selected from CF_3 , OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;

10 alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

15 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

20 R^{3b} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3c} , at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

A is selected from:

30 C_{3-10} carbocyclic residue substituted with 0-2 R^4 , and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

A^1 is H or A;

alternatively, A and A¹ and the carbon to which they are attached combine to form fluorene;

A² is selected from H, A, and CHA¹A⁴;

5

A³ is selected from H, A, C₁₋₄ alkyl, and -(CH₂)_rNR²R^{2a};

A⁴ is H or A;

10 B is selected from: H, Y, and X-Y

X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -CR²(NR^{1'}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -OS(O)₂-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;

15

20

Y is selected from:

(CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,

25 C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

30 alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a},

$C(=NR^2)NR^2R^{2a}$, $C(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$,
 $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$
 alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $NHCH_2R^{1''}$, $OCH_2R^{1''}$,
 $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and
 5 $S(CH_2)_2(CH_2)_tR^{1'}$;

alternatively, one R^4 is a 5-6 membered aromatic heterocycle
 containing from 1-4 heteroatoms selected from the group
 consisting of N, O, and S;

10

R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$,
 $(CH_2)_rF$, $(CH_2)_rBr$, $(CH_2)_rCl$, Cl, Br, F, I, C_{1-4} alkyl,
 -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$,
 $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)R^{3c}$,
 15 $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$,
 $NR^2SO_2-C_{1-4}$ alkyl, $C(O)NHSO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$,
 $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle
 20 containing from 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-1 R^5 ;

R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$,
 F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$,
 25 $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$,
 $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$,
 $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl,
 $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;

30 R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl,
 phenyl substituted with 0-2 R^6 , and benzyl substituted
 with 0-2 R^6 ;

R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$,
halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$,
 $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$,
5 $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7 , at each occurrence, is selected from H, OH, C_{1-6} alkyl,
 C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl,
 $(CH_2)_n$ -phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10}
10 arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4}
alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4}
alkoxycarbonyl, C_{1-6} alkylaminocarbonyl,
phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

15 R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and
 $(CH_2)_n$ -phenyl;

alternatively, R^7 and R^8 combine to form a 5 or 6 membered
saturated, ring which contains from 0-1 additional
20 heteroatoms selected from the group consisting of N, O,
and S;

R^9 , at each occurrence, is selected from H, C_{1-6} alkyl and
 $(CH_2)_n$ -phenyl;

25 R^{10} is selected from H, phenyl substituted with 0-2 R^{10a} , and
naphthyl substituted with 0-2 R^{10a} ;

n , at each occurrence, is selected from 0, 1, 2, and 3;

30 m , at each occurrence, is selected from 0, 1, and 2;

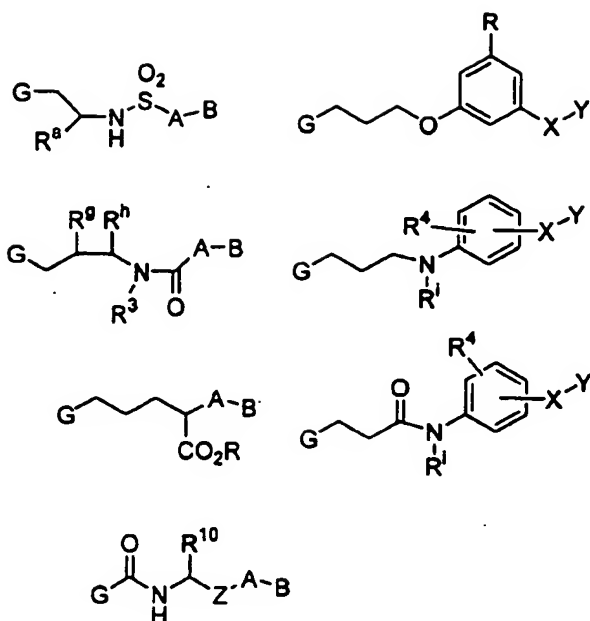
p , at each occurrence, is selected from 0, 1, and 2;

s, at each occurrence, is selected from 0, 1, and 2; and,

5 t, at each occurrence, is selected from 0, 1, 2, and 3.

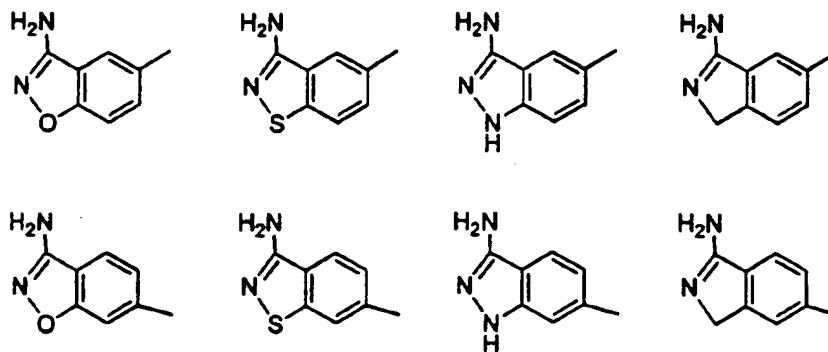
Chemical structures 1-10 are defined as follows:

- Structure 1:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $B-A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 2:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $B-A-Z$. The five-membered ring contains a sulfur atom (S) and a nitrogen atom (N) substituted with a group L_n-G .
- Structure 3:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $B-A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 4:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 5:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 6:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 7:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 8:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 9:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .
- Structure 10:** A bicyclic system consisting of a six-membered ring fused to a five-membered ring. The six-membered ring contains a carbonyl group (C=O) and a nitrogen atom (N) substituted with a group $A-Z$. The five-membered ring contains a nitrogen atom (N) substituted with a group L_n-G .

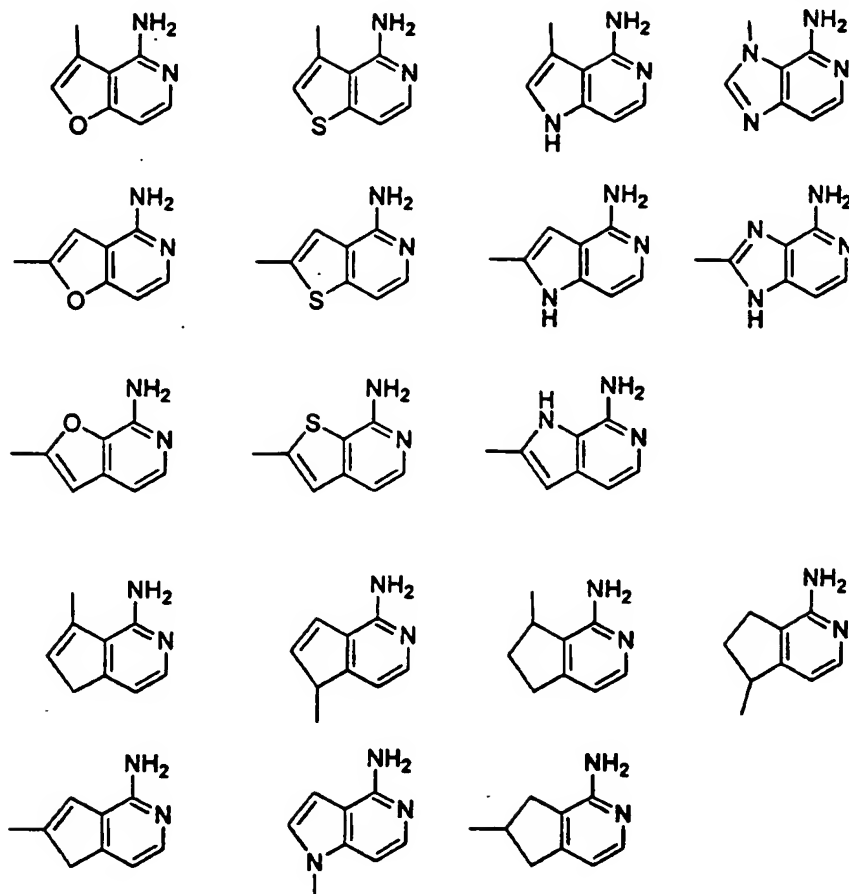


or a stereoisomer or pharmaceutically acceptable salt
5 thereof, wherein;

G is selected from the group:



10



- 5 L_n is a linker which is absent or is selected from O, S, CH_2 , $\text{*CH}_2\text{NHC(O)}$, $\text{*CH(R}^a\text{)NHC(O)}$, $\text{*CH}_2\text{NHC(O)CH}_2$, and $\text{*CH(R}^a\text{)NHC(O)CH}_2$, provided that L_n and M do not form an O-N or S-N bond and the * indicates where L_n is bonded to G;

10

M^1 is absent or is CHR;

M^2 is N or CR^f ;

15

M^3 is N or CR^d ;

provided that only one of M^2 and M^3 is N;

R^a is selected from C(O)C(O)OR³, C(O)C(O)NR²R^{2a}, and C(O)-A;

R^b is selected from H, R, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;

5

R^c is selected from H and C₁₋₆ alkyl;

alternatively, R^b and R^c together are -(CH₂)₄-;

10

R^d is selected from H, F, and Cl;

15

R^e is selected from H, N(CH₃)(CH₂CO₂H) and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴);

alternatively, R^d and R^e combine to form -NR³-C(O)-C(R^{1b}R³)-NR³- or -N=CR²-NR³-;

20

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form -NR³-C(R^{1b}R³)-C(O)-NR³- or -NR³-CR²=N-;

25

R^g is selected from H, CH₂OR³, CH₂C(O)OR³, C₁₋₄ alkyl, C(O)NH₂, and NH₂;

R^h is selected from H, CH₂-phenyl, CH₂CH₂-phenyl, and CH=CH-phenyl;

30

Rⁱ is selected from SO₂CH₂C(O)OR³, C(O)CH₂C(O)OR³, and C(O)OR³;

R is selected from H, Cl, F, Br, I, $(\text{CH}_2)_t\text{OR}^3$, C_{1-4} alkyl, benzyl, OCF_3 , CF_3 , $\text{C}(\text{O})\text{NR}^7\text{R}^8$, and $(\text{CR}^8\text{R}^9)_t\text{NR}^7\text{R}^8$;

Z is selected from a $(\text{CR}^8\text{R}^9)_{1-4}$, $(\text{CR}^8\text{R}^9)_r\text{O}(\text{CR}^8\text{R}^9)_r$,

- 5 $(\text{CR}^8\text{R}^9)_r\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{OC}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{OC}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$,
 $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{C}(\text{O})\text{O}(\text{CR}^8\text{R}^9)_r$, $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CR}^8\text{R}^9)_r$,
10 $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_p(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{S}(\text{O})_2(\text{CH}=\text{CH})$,
 $(\text{CCR}^8\text{R}^9)_r\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2(\text{CR}^8\text{R}^9)_r$, and
 $(\text{CR}^8\text{R}^9)_r\text{NR}^3\text{SO}_2\text{NR}^3(\text{CR}^8\text{R}^9)_r$, provided that Z does not form
a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with the
groups to which Z is attached;

15

R^{1a} is absent or selected from $-(\text{CH}_2)_r\text{R}^{1'}$, $-\text{CH}=\text{CH}-\text{R}^{1'}$,
 $\text{NHCH}_2\text{R}^{1''}$, $\text{OCH}_2\text{R}^{1''}$, $\text{SCH}_2\text{R}^{1''}$, $\text{NH}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$,
 $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$;

- 20 $\text{R}^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO,
 $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OR}^2$, NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $\text{OC}(\text{O})\text{R}^2$,
 $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$, $\text{S}(\text{O})_p(\text{CH}_2)_r\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$,
 $\text{C}(=\text{NR}^{2c})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$,
 $\text{OC}(\text{O})\text{NR}^{2a}\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$,
25 $\text{NR}^2\text{SO}_2\text{R}^{2b}$, C_{3-6} carbocyclic residue substituted with 0-2
 R^4 , and 5-10 membered heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting
of N, O, and S substituted with 0-2 R^4 ;

- 30 $\text{R}^{1''}$ is selected from H, $\text{CH}(\text{CH}_2\text{OR}^2)_2$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
 $\text{S}(\text{O})\text{R}^{2b}$, $\text{S}(\text{O})_2\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with A;

5 R², at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

10

R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ cycloalkylmethyl substituted with 0-2 R^{4b}, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

15

R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

20

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

25

30

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1

additional heteroatoms selected from the group
consisting of N, O, and S;

5 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and
phenyl;

R^{3a} , at each occurrence, is selected from H, C_{1-4} alkyl, and
phenyl;

10 R^{3b} , at each occurrence, is selected from H, C_{1-4} alkyl, and
phenyl;

R^{3c} , at each occurrence, is selected from C_{1-4} alkyl, and
phenyl;

15

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^4 , and
5-10 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O, and
20 S substituted with 0-2 R^4 ;

A^1 is H or A;

alternatively, A and A^1 and the carbon to which they are
25 attached combine to form fluorene;

A^2 is selected from H, A, and CH_2A^4 ;

A^3 is selected from H, A, C_{1-4} alkyl, and $-(CH_2)_tNR^2R^{2a}$;

30

A^4 is H or A;

B is selected from: H, Y, and X-Y

35 X is selected from C_{1-4} alkylene, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$,
 $-CR^2(NR^{1''}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$,

$-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_p-$, $-\text{S}(\text{O})_p\text{CR}^2\text{R}^{2a}-$,
 $-\text{CR}^2\text{R}^{2a}\text{S}(\text{O})_p-$, $-\text{S}(\text{O})_2\text{NR}^2-$, $-\text{NR}^2\text{S}(\text{O})_2-$, $-\text{NR}^2\text{S}(\text{O})_2\text{CR}^2\text{R}^{2a}-$,
 $-\text{CR}^2\text{R}^{2a}\text{S}(\text{O})_2\text{NR}^2-$, $-\text{NR}^2\text{S}(\text{O})_2\text{NR}^2-$, $-\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2\text{C}(\text{O})-$,
 $-\text{C}(\text{O})\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{NR}^2\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})\text{NR}^2-$,
5 $-\text{CR}^2\text{R}^{2a}\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{NR}^2-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$,
 $-\text{NR}^2-$, $-\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2-$, O , $-\text{CR}^2\text{R}^{2a}\text{O}-$, and
 $-\text{OCR}^2\text{R}^{2a}-$;

Y is selected from:

10 $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, provided that X-Y do not form a N-N, O-N, or S-N bond,

C_{3-10} carbocyclic residue substituted with 0-2 R^{4a} , and
5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and
15 S substituted with 0-2 R^{4a} ;

alternatively, Z-A-B combine to form S- C_{1-6} alkyl;

R^4 , at each occurrence, is selected from H, =O, $(\text{CH}_2)_r\text{OR}^2$, F,
20 Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
 $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NS}(\text{O})_2\text{R}^5)\text{NR}^2\text{R}^{2a}$, $\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$,
 $\text{C}(\text{O})\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2-\text{C}_{1-4}$
alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$, $\text{S}(\text{O})_p\text{R}^5$, $(\text{CF}_2)_r\text{CF}_3$, $\text{NHCH}_2\text{R}^{1''}$, $\text{OCH}_2\text{R}^{1''}$,
25 $\text{SCH}_2\text{R}^{1''}$, $\text{N}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and
 $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$;

alternatively, one R^4 is a 5-6 membered aromatic heterocycle
containing from 1-4 heteroatoms selected from the group
30 consisting of N, O, and S;

R^{4a} , at each occurrence, is selected from H, =O, $(\text{CH}_2)_r\text{OR}^2$,
 $(\text{CH}_2)_r\text{-F}$, $(\text{CH}_2)_r\text{-Br}$, $(\text{CH}_2)_r\text{-Cl}$, Cl, Br, F, I, C_{1-4} alkyl,

-CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b},
 C(O)NR²R^{2a}, C(O)NH(CH₂)₂NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)R^{3c},
 C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a},
 NR²SO₂-C₁₋₄ alkyl, C(O)NHSO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
 5 S(O)_pR⁵, and (CF₂)_rCF₃;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle
 containing from 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-1 R⁵;

10

R^{4b}, at each occurrence, is selected from H, =O, (CH₂)_rOR³,
 F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR³R^{3a},
 (CH₂)_rC(O)R³, (CH₂)_rC(O)OR^{3c}, NR³C(O)R^{3a}, C(O)NR³R^{3a},
 NR³C(O)NR³R^{3a}, C(=NR³)NR³R^{3a}, NR³C(=NR³)NR³R^{3a}, SO₂NR³R^{3a},
 15 NR³SO₂NR³R^{3a}, NR³SO₂-C₁₋₄ alkyl, NR³SO₂CF₃, NR³SO₂-phenyl,
 S(O)_pCF₃, S(O)_p-C₁₋₄ alkyl, S(O)_p-phenyl, and (CF₂)_rCF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
 phenyl substituted with 0-2 R⁶, and benzyl substituted
 20 with 0-2 R⁶;

R⁶, at each occurrence, is selected from H, OH, (CH₂)_rOR²,
 halo, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b},
 NR²C(O)R^{2b}, NR²C(O)NR²R^{2a}, C(=NH)NH₂, NHC(=NH)NH₂,
 25 SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, and NR²SO₂C₁₋₄ alkyl;

R⁷, at each occurrence, is selected from H, OH, C₁₋₆ alkyl,
 C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₄ alkoxycarbonyl,
 (CH₂)_n-phenyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxycarbonyl, C₆₋₁₀
 30 arylmethylcarbonyl, C₁₋₄ alkylcarbonyloxy C₁₋₄
 alkoxycarbonyl, C₆₋₁₀ arylcarbonyloxy C₁₋₄

alkoxycarbonyl, C₁₋₆ alkylaminocarbonyl,
phenylaminocarbonyl, and phenyl C₁₋₄ alkoxycarbonyl;

5 R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and
(CH₂)_n-phenyl;

alternatively, R⁷ and R⁸ combine to form a 5 or 6 membered
saturated, ring which contains from 0-1 additional
heteroatoms selected from the group consisting of N, O,
10 and S;

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and
(CH₂)_n-phenyl;

15 R¹⁰ is selected from H, phenyl substituted with 0-2 R^{1a}, and
naphthyl substituted with 0-2 R^{1a};

n, at each occurrence, is selected from 0, 1, 2, and 3;

20 m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

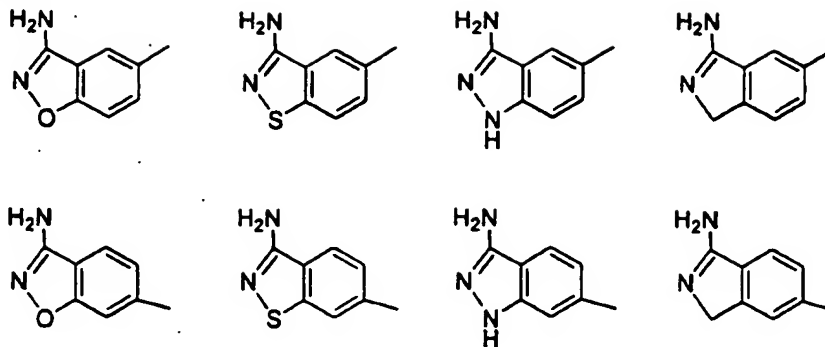
25 s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

30

4. A compound according to Claim 3, wherein:

G is selected from the group:



R is selected from H, Cl, F, Br, I, $(\text{CH}_2)_t\text{OR}^3$, C_{1-4} alkyl, OCF_3 , CF_3 , $\text{C}(\text{O})\text{NR}^7\text{R}^8$, and $(\text{CR}^8\text{R}^9)_t\text{NR}^7\text{R}^8$;

5

Z is selected from a CH_2O , OCH_2 , CH_2NH , NHCH_2 , $\text{C}(\text{O})$, $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{NHC}(\text{O})$, $\text{C}(\text{O})\text{NH}$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$, SO_2NH , and NHSO_2 , provided that Z does not form a N-N, N-O, NCH_2N , or NCH_2O bond with ring M or group A;

10

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4 ;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

25

B is selected from: H, Y, and X-Y;

X is selected from C₁₋₄ alkylene, -C(O)-, -C(=NR)-,

-CR²(NR²R^{2a})-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -C(O)NR²-,

-NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-,

-CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)NR²-, -NR²-,

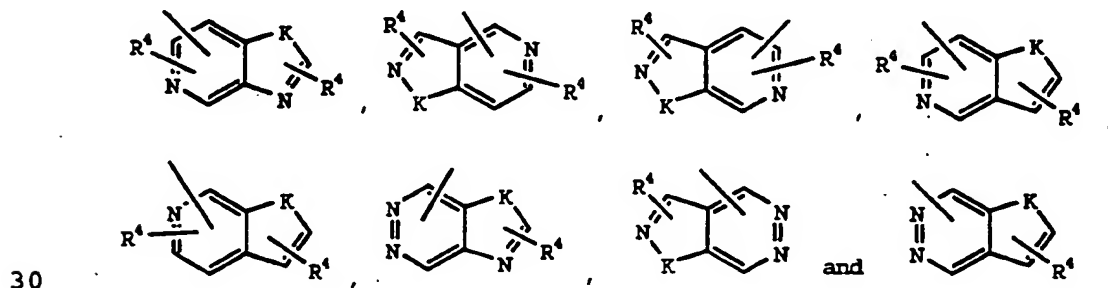
5 -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O-, -CR²R^{2a}O-, and -OCR²R^{2a}-;

Y is NR²R^{2a} or CH₂NR²R^{2a}, provided that X-Y do not form a N-N
or O-N bond;

10 alternatively, Y is selected from one of the following
carbocyclic and heterocyclic systems which are
substituted with 0-2 R^{4a};

cyclopropyl, cyclopentyl, cyclohexyl, phenyl,
piperidiny, piperaziny, pyridyl, pyrimidyl, furanyl,
15 morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,
oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,
isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,
20 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,
1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
benzothiofuranyl, indolyl, benzimidazolyl,
25 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,
benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic
heteroaryl ring systems:

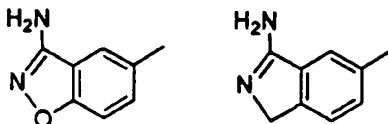


K is selected from O, S, NH, and N.

5. A compound according to Claim 4, wherein:

5

G is selected from:



10 Z is C(O)CH₂ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R⁴; and,

15 B is selected from Y, X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

B is selected from: Y and X-Y;

20 X is selected from CH₂, -C(O)-, and O;

Y is NR²R^{2a} or CH₂NR²R^{2a}, provided that X-Y does not form an O-N bond;

25 alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

30 phenyl, piperazinyl, pyridyl, pyrimidyl, morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-triazolyl;

R², at each occurrence, is selected from H, CF₃, CH₃, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, CF₃, CH₃,
CH(CH₃)₂, cyclopropylmethyl, benzyl, and phenyl;

alternatively, R² and R^{2a} combine to form a ring system

5 substituted with 0-2 R^{4b}, the ring system being selected
from pyrrolidinyl, piperazinyl and morpholino;

R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², Cl,
F, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;

10

R^{4a} is selected from Cl, F, C₁₋₄ alkyl, CF₃, (CH₂)_rNR²R^{2a},
S(O)_pR⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

R^{4b}, at each occurrence, is selected from OH, Cl, F, CH₃, and
15 CF₃;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl, and benzyl;

20 R⁷, at each occurrence, is selected from H, CH₃, and CH₂CH₃;
and,

R⁸, at each occurrence, is selected from H and CH₃.

25

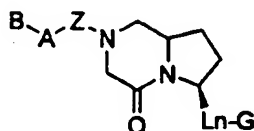
6. A compound according to Claim 5, wherein:

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl,
2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-
30 phenyl, 2-methylphenyl, 2-aminophenyl, and 2-
methoxyphenyl; and,

B is selected from the group: 2-CF₃-phenyl, 2-
(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl,
35 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl,

2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(isopropylaminomethyl)phenyl, 2-(cyclopropylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 2-(3-hydroxy-N-pyrrolidinylmethyl)phenyl, 4-morpholino, 2-(1'-CF₃-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-(N,N-dimethylaminomethyl)imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

7. A compound according to Claim 3, wherein the compound is of the formula:



L_n is $^*CH_2NHC(O)CH_2$ or $^*CH(R^a)NHC(O)CH_2$, the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

Z is selected from a C₁₋₄ alkylene, (CH₂)_rC(O), and (CH₂)_rS(O)₂;

R^2 , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2b} , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

- R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;
- 5 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;
- A is C_{5-6} carbocyclic residue substituted with 0-2 R^4 ;
- 10 R^4 , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;
- 15 R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl, and benzyl;
- p, at each occurrence, is selected from 0, 1, and 2; and,
- 20 r, at each occurrence, is selected from 0, 1, 2, and 3.

8. A compound according to Claim 7, wherein:

- 25 L_n is $*CH(R^a)NHC(O)CH_2$;

R^a is $C(O)C(O)OH$;

Z is selected from a CH_2 , $(CH_2)_2C(O)$, and $CH_2S(O)_2$;

30

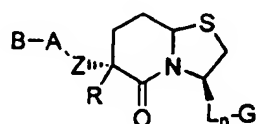
A is cyclohexyl or phenyl and is substituted with 0-1 R^4 ;

R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 ,
F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$,
 $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

5 r , at each occurrence, is selected from 0, 1, and 2.

9. A compound according to Claim 3, wherein the
compound is of the formula:

10



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates
where L_n is bonded to G;

15

R^a is $C(O)C(O)OR^3$;

R is H or NH_2 ;

20 Z is selected from a C_{1-4} alkylene, $(CH_2)_rC(O)$, and
 $(CH_2)_rS(O)_2$;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

25

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl,
benzyl, and phenyl;

R^{2b} , at each occurrence, is selected from H, C_{1-6} alkyl,
30 benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃,
CH₃, benzyl, and phenyl;

5 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
phenyl;

A is a C₅₋₆ carbocyclic residue substituted with 0-2 R⁴;

10 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵,
and CF₃;

15 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

20 r, at each occurrence, is selected from 0, 1, 2, and 3.

10. A compound according to Claim 3, wherein:

25 L_n is *CH(R^a)NHC(O)CH₂;

R is H;

R^a is C(O)C(O)OH;

30 Z is selected from a CH₂, (CH₂)₂C(O), and CH₂S(O)₂;

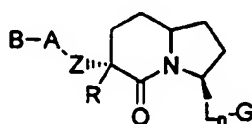
A is cyclohexyl or phenyl and is substituted with 0-1 R⁴;

R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 ,
 F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$,
 $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

5 r , at each occurrence, is selected from 0, 1, 2, and 3.

11. A compound according to Claim 3, wherein the
 compound is of the formula:

10



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates
 where L_n is bonded to G;

15

R is H or NH_2 ;

R^a is $C(O)C(O)OR^3$;

20 Z is C_{1-4} alkylene;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl,
 benzyl, and phenyl;

25 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl,
 benzyl, and phenyl;

R^{2b} , at each occurrence, is selected from H, C_{1-6} alkyl,
 benzyl, and phenyl;

30

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 ,
 CH_3 , benzyl, and phenyl;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is phenyl substituted with 0-2 R⁴;

5

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

10 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

15 r, at each occurrence, is selected from 0, 1, 2, and 3.

12. A compound according to Claim 11, wherein:

20 L_n is *CH(R^a)NHC(O)CH₂;

R is NH₂;

R^a is C(O)C(O)OH;

25

Z is CH₂;

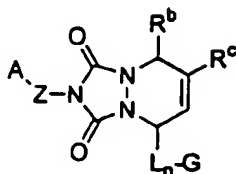
A is phenyl substituted with 0-1 R⁴;

30 R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

35

13. A compound according to Claim 3, wherein the compound is of the formula:



5

L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the $*$ indicates where L_n is bonded to G;

R^a is selected from $C(O)C(O)OR^3$ and $C(O)-A$;

10

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

15 alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8R^9)_{1-4}$;

R^2 , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

20

R^{2a} , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

25 R^{2b} , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

30

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

5 C₆₋₁₀ aromatic carbocyclic residue substituted with 0-2 R⁴, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

10

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

15 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

20

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

p, at each occurrence, is selected from 0, 1, and 2;

25

r, at each occurrence, is selected from 0, 1, 2, and 3.

14. A compound according to Claim 13, wherein:

30

L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);

35

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

5 alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8H)_{1-2}$;

10 A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R^4 ;

R^4 , at each occurrence, is selected from H, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

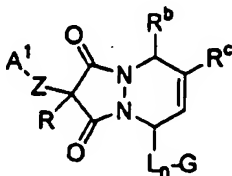
15

R^8 , at each occurrence, is selected from H, methyl and phenyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

20

15. A compound according to Claim 3, wherein the compound is of the formula:



25

L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the * indicates where L_n is bonded to G;

R^a is selected from $C(O)C(O)OR^3$ and $C(O)-A$;

30

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

5

R is selected from H, benzyl, C_{1-4} alkyl, and NH_2 ;

Z is $(CR^8R^9)_{1-4}$;

10 R^2 , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

R^{2a} , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

15

R^{2b} , at each occurrence, is selected from H, CF_3 , and C_{1-6} alkyl;

20 R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

25 A is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^4 , and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

30

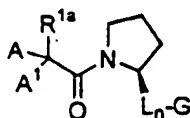
R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

- R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;
- R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;
- R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;
- p, at each occurrence, is selected from 0, 1, and 2;
- r, at each occurrence, is selected from 0, 1, 2, and 3.
16. A compound according to Claim 15, wherein:
- L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;
- R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);
- R^b is selected from H, phenyl, C₁₋₁₀ alkyl, and C₂₋₅ alkenyl;
- R^c is selected from H and C₁₋₆ alkyl;
- alternatively, R^b and R^c together are -(CH₂)₄-;
- Z is (CR⁸H)₁₋₂;
- A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R⁴;
- R⁴, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R^8 , at each occurrence, is selected from H, C₁₋₆ alkyl and phenyl;

5 r , at each occurrence, is selected from 0, 1, and 2.

17. A compound according to Claim 16, wherein:



10

L_n is $^*CH_2NHC(O)$ or $^*CH(R^a)NHC(O)$ and the * indicates where L_n is bonded to G;

R^{1a} is selected from $-(CH_2)_r-R^{1'}$ and $NHCH_2R^{1''}$;

15

$R^{1'}$ is selected from H, OR^2 , NR^2R^{2a} , and $NR^2SO_2(CH_2)_rR^{2b}$;

$R^{1''}$ is selected from $C(O)NR^2R^{2a}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

20 R^2 , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

25

R^{2b} , at each occurrence, is selected from C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, phenyl substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;

30

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is phenyl substituted with 0-2 R^4 ;

A^1 is H or A;

alternatively, A and A^1 and the carbon to which they are attached combine to form fluorene;

A^2 is selected from H, A, and $CH_2A^3A^4$;

A^3 is selected from H, A, C_{1-4} alkyl, and $-(CH_2)_rNR^2R^{2a}$;

A^4 is H or A;

R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

R^{4b} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

5

18. A compound according to Claim 17, wherein:

L_n is $^*\text{CH}_2\text{NHC(O)}$ and the * indicates where L_n is bonded to G;

10

R^{1a} is selected from $-(\text{CH}_2)_r\text{-R}^{1'}$ and $\text{NHCH}_2\text{R}^{1''}$;

$R^{1'}$ is selected from OH, NR^2R^{2a} , and $\text{NR}^2\text{SO}_2(\text{CH}_2)_r\text{R}^{2b}$;

15 $R^{1''}$ is selected from $\text{C(O)NR}^2\text{R}^{2a}$, $\text{S(O)}_2\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

20 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b} , at each occurrence, is selected from C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, phenyl substituted with 0-1 R^{4b} , and
25 pyrrolidinyl substituted with 0-1 R^{4b} ;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

30 alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a piperidine ring substituted with 0-1 R^{4b} ;

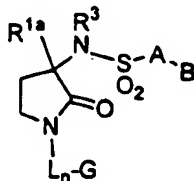
R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

5 R^{4b} , at each occurrence, is selected from H, =O, OH, F, Cl, C_{1-4} alkyl, and NH_2 ; and,

r , at each occurrence, is selected from 0, 1, and 2.

10

19. A compound according to Claim 3, wherein the compound is of the formula:



15 L_n is CH_2 ;

R^{1a} is $-(CH_2)_r-R^{1'}$;

20 $R^{1'}$ is selected from H, C_{1-3} alkyl, $(CH_2)_rOR^2$, NR^2R^{2a} , $C(O)R^{2c}$, phenyl substituted with 0-2 R^4 , and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

25 R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

30

- R^{2b} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;
- R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 ,
5 CH_3 , benzyl, and phenyl;
- R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;
- 10 A is selected from:
 C_{6-10} aromatic ring substituted with 0-2 R^4 , and
5-10 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^4 ;
- 15 B is selected from: H, Y, and X-Y
- X is selected from C_{1-4} alkylene, $-NR^2-$, and O;
- 20 Y is selected from:
 C_{6-10} aromatic ring substituted with 0-2 R^{4a} , and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a} ;
- 25 R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, Cl,
Br, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$,
 $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;
- 30 R^{4a} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, Cl,
Br, F, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$,
 $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$,
and CF_3 ;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

20. A compound according to Claim 19, wherein:

R^{1a} is -(CH₂)_r-R^{1'};

R^{1'} is selected from H, C₁₋₃ alkyl, OH, NR²R^{2a}, and phenyl substituted with 0-2 R⁴;

A is selected from:

phenyl substituted with 0-2 R⁴, naphthyl substituted with 0-2 R⁴, thienyl substituted with 0-2 R⁴, benzothienyl substituted with 0-2 R⁴, 5-aza-benzothienyl substituted with 0-2 R⁴, 6-azabenzothienyl substituted with 0-2 R⁴, and quinolinyl substituted with 0-2 R⁴;

B is selected from: H, Y, and X-Y

X is O;

Y is phenyl substituted with 0-1 R^{4a};

R⁴, at each occurrence, is selected from H, OR², CH₂OR², F,

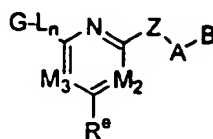
Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃;

R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F,

Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

- 5 21. A compound according to Claim 3, wherein the compound is of the formula:



L_n is O or S;

10

M^2 is N or CR^f ;

M^3 is N or CR^d ;

- 15 provided that only one of M^2 and M^3 is N;

R^e is selected from H, $\text{N}(\text{CH}_3)(\text{CH}_2\text{CO}_2\text{H})$ and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

20

R^d is selected from H, F, and Cl;

alternatively, R^d and R^e combine to form $-\text{NR}^3-\text{C}(\text{O})-\text{C}(\text{R}^1\text{R}^3)-$
 NR^3- or $-\text{N}=\text{CR}^2-\text{NR}^3-$;

25

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form $-\text{NR}^3-\text{C}(\text{R}^1\text{R}^3)-\text{C}(\text{O})-$
 NR^3- or $-\text{NR}^3-\text{CR}^2=\text{N}-$;

30

Z is O, provided that Z does not form a N-O or NCH_2O bond with the groups to which Z is attached;

R^{1b} is selected from H, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with A;

5 R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

10 R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

15 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

20 C₅₋₆ carbocyclic residue substituted with 0-2 R⁴, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

25 B is H or Y;

Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

30

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},

$(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$,
 $\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, and CF_3 ;

R^{4a} , at each occurrence, is selected from H, =O, $(\text{CH}_2)_r\text{OR}^2$,
 5 $(\text{CH}_2)_r\text{-F}$, $(\text{CH}_2)_r\text{-Br}$, $(\text{CH}_2)_r\text{-Cl}$, Cl, Br, F, I, C₁₋₄ alkyl,
 $-\text{CN}$, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$,
 $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, and
 CF_3 ; and,

10 r , at each occurrence, is selected from 0, 1, 2, and 3.

22. A compound according to Claim 21, wherein:

15 L_n is O;

R^e is $\text{N}(\text{CH}_3)(\text{CH}_2\text{CO}_2\text{H})$;

R^d is H or F;

20

alternatively, R^d and R^e combine to form $-\text{NR}^3-\text{C}(\text{O})-\text{C}(\text{R}^{1b}\text{R}^3)-$
 NR^3- or $-\text{N}=\text{CR}^2-\text{NR}^3-$;

R^f is H or F;

25

alternatively, R^e and R^f combine to form $-\text{NR}^3-\text{C}(\text{R}^{1b}\text{R}^3)-\text{C}(\text{O})-$
 NR^3- or $-\text{NR}^3-\text{CR}^2=\text{N}-$;

R^{1b} is selected from H, C₁₋₂ alkyl and benzyl;

30

A is phenyl substituted with 0-2 R^4 ;

B is H or Y;

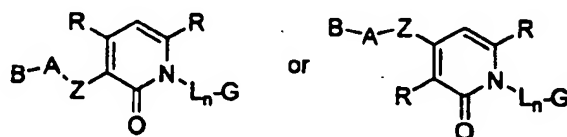
Y is 5 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

5 R⁴, at each occurrence, is selected from H, C₁₋₄ alkyl, and NR²R^{2a}; and,

R^{4a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and NR²R^{2a}.

10

23. A compound according to Claim 3, wherein the compound is of the formula:



15

L_n is *CH₂NHC(O)CH₂ or *CH(R^a)NHC(O)CH₂ and the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OR³;

20

R, at each occurrence, is selected from H, Cl, F, Br, I, OR³, C₁₋₄ alkyl, C(O)NH₂, and NH₂;

Z is selected from a C₁₋₄ alkylene and (CH₂)_rSO₂NR³;

25

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

30

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

5 R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^4 , and
5-6 membered aromatic heterocyclic system containing
10 from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;

B is selected from: H, Y, and X-Y

15 alternatively, when B is H, A is (phenyl)₂CH- substituted with 0-2 R^4 ;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-NR^2-$, and O;

20 Y is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^{4a} , and
5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a} ;

25

R^4 , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

30 R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, $-CN$, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

24. A compound according to Claim 23, wherein:

5 L_n is $^*\text{CH}_2\text{NHC(O)CH}_2$ and the * indicates where L_n is bonded to G;

R, at each occurrence, is selected from H and C_{1-4} alkyl;

10 Z is $\text{CH}_2\text{SO}_2\text{NR}^3$;

A is phenyl substituted with 0-2 R^4 ;

B is H;

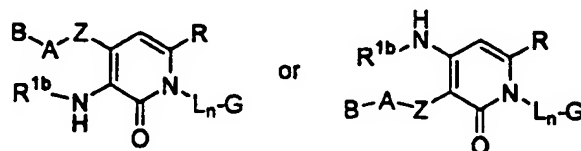
15

R^4 , at each occurrence, is selected from H, $(\text{CH}_2)_r\text{OR}^2$, F, Cl, C_{1-4} alkyl, $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{C(O)R}^{2c}$, and $\text{C(O)NR}^2\text{R}^{2a}$; and,

20 r, at each occurrence, is selected from 0, 1, and 2.

25 25. A compound according to Claim 3, wherein the compound is of the formula:

25



L_n is $^*\text{CH}_2\text{NHC(O)CH}_2$ or $^*\text{CH(R}^a\text{)NHC(O)CH}_2$ and the * indicates where L_n is bonded to G;

30 R^a is C(O)C(O)OR^3 ;

R, at each occurrence, is selected from H, C_{1-4} alkyl, and NH_2 ;

R^{1b} is H or C₁₋₆ alkyl;

Z is selected from a C₁₋₄ alkylene and (CH₂)_rS(O)_p(CH₂)_r;

5

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,

10

benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

15 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

C₃₋₆ carbocyclic residue substituted with 0-2 R⁴, and

20

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

B is selected from: H, Y, and X-Y

25

alternatively, when B is H, A is (phenyl)₂CH- substituted with 0-2 R⁴;

X is selected from C₁₋₄ alkylene, -C(O)-, -NR²-, and O;

30

Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of

35

N, O, and S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

5 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F,
Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

10 R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
(CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

p is selected from 0, 1, and 2; and,

15 r, at each occurrence, is selected from 0, 1, 2, and 3.

26. A compound according to Claim 25, wherein:

20 L_n is *CH₂NHC(O)CH₂ and the * indicates where L_n is bonded to
G;

R is H or C₁₋₄ alkyl;

25 R^{1b} is H;

Z is CH₂, CH₂S, or CH₂S(O)₂;

A is a C₃₋₆ carbocyclic residue substituted with 0-2 R⁴;

30 B is H

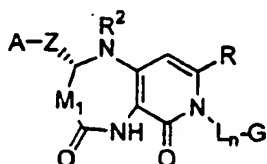
alternatively, Z-A-B combine to form S-C₁₋₆ alkyl;

R^4 , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

5 r , at each occurrence, is selected from 0, 1, and 2.

27. A compound according to Claim 3, wherein the compound is of the formula:

10



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the $*$ indicates where L_n is bonded to G;

15 M^1 is absent or is CHR;

R is selected from H, Cl, F, Br, I, OR^3 , C_{1-4} alkyl, OCF_3 , CF_3 , and NH_2 ;

20 Z is C_{1-4} alkylene;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

25 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

30

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

5 C₃₋₆ carbocyclic residue substituted with 0-2 R⁴, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

10 R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

15

28. A compound according to Claim 27, wherein:

L_n is *CH₂NHC(O)CH₂ and the * indicates where L_n is bonded to
20 G;

M¹ is absent;

R is selected from H and C₁₋₄ alkyl;

25

Z is CH₂;

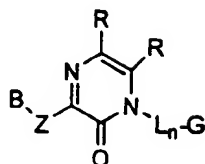
A is C₃₋₆ carbocyclic residue substituted with 0-1 R⁴;

30 R⁴, at each occurrence, is selected from H, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and CF₃; and,

r, at each occurrence, is selected from 0, 1, and 2.

35

29. A compound according to Claim 3, wherein the compound is of the formula:



5 L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

10 R, at each occurrence, is selected from H, Cl, F, Br, I, OR^3 , C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

Z is $(CHR^8)NR^3$, $(CHR^8)_2NR^3$, and $(CHR^8)_2SO_2R^3$;

15 provided that when Z is $(CHR^8)_2NR^3$, then B is absent;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

20 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

25

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

30

B is H or Y;

Y is selected from:

C₅₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and
5 5-6 membered heterocyclic system containing from 1-2
heteroatoms selected from the group consisting of N, O, and
S substituted with 0-2 R^{4a};

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
Cl, Br, F, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a},
10 (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and
phenyl; and,

15 r, at each occurrence, is selected from 0, 1, 2, and 3.

30. A compound according to Claim 29, wherein:

20 L_n is *CH₂NHC(O)CH₂ and the * indicates where L_n is bonded to
G;

R, at each occurrence, is selected from H and C₁₋₄ alkyl;

25 Z is (CH₂)₂NR³, (CHR⁸)₂NR³ or (CHR⁸)₂SO₂R³;

B is H or Y;

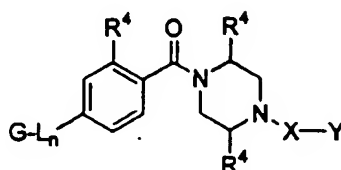
Y is phenyl substituted with 0-1 R⁴, pyridyl substituted
30 with 0-1 R⁴ or N-morpholino substituted with 0-1 R⁴;

R⁴, at each occurrence, is selected from H, and C₁₋₄ alkyl;

R⁸, at each occurrence, is selected from H, methyl and
35 phenyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

- 5 31. A compound according to Claim 3, wherein the compound is of the formula:



L_n is absent;

10

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

15

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

20 X is SO_2 or $SO_2(CH=CH)$;

Y is selected from:

C_{6-10} carbocyclic residue substituted with 0-2 R^{4a} , and
5-6 membered aromatic heterocyclic system containing
25 from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 ,
F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$,
30 $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ;

R^{4a} , at each occurrence, is selected from H, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

5 r , at each occurrence, is selected from 0, 1, 2, and 3.

32. A compound according to Claim 31, wherein:

10 X is SO_2 ;

Y is selected from phenyl substituted with 0-2 R^{4a} and naphthyl substituted with 0-2 R^{4a} ;

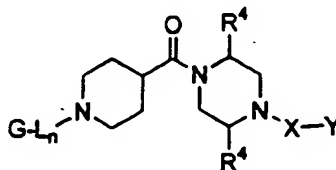
15 R^4 , at each occurrence, is selected from H, =O, OH, CH_2OH , F, Cl, Br, C_{1-4} alkyl, $C(O)NR^2R^{2a}$, and $C(O)R^{2c}$;

R^{4a} , at each occurrence, is selected from H, OH, CH_2OH , F, Cl, Br, C_{1-4} alkyl, and $C(O)R^{2c}$; and,

20

r , at each occurrence, is selected from 0, 1, and 2.

33. A compound according to Claim 3, wherein the
25 compound is of the formula:



L_n is absent;

30

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

- 5 R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered
10 saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

X is SO₂ or SO₂(CH=CH);

15

Y is selected from:

C₆₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of
20 N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

25

R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

30 r, at each occurrence, is selected from 0, 1, 2, and 3.

34. A compound according to Claim 33, wherein:

35 X is SO₂;

Y is phenyl substituted with 0-2 R^{4a} or naphthyl substituted with 0-2 R^{4a} ;

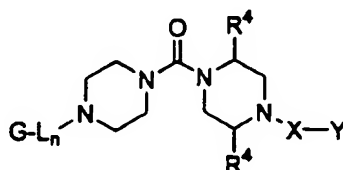
5 R^4 , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, NH_2 , $(CH_2)_rC(O)R^{2c}$, and $C(O)NR^2R^{2a}$;

R^{4a} , at each occurrence, is selected from H, =O, OR^2 , CH_2OR^2 ,
10 F, Cl, Br, I, C_{1-4} alkyl, NH_2 , $(CH_2)_rC(O)R^{2c}$, and $C(O)NR^2R^{2a}$;

r, at each occurrence, is selected from 0, 1, 2, and 3.

15

35. A compound according to Claim 3, wherein the compound is of the formula:



20 L_n is absent;

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

25 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

30

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered

saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

5 X is SO₂ or SO₂(CH=CH);

Y is selected from:

C₆₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
5-6 membered aromatic heterocyclic system containing
10 from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
15 C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

R^{4a}, at each occurrence, is selected from H, OR², CH₂OR², F,
Cl, Br, I, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

20

r, at each occurrence, is selected from 0, 1, 2, and 3.

36. A compound according to Claim 35, wherein:

25

X is SO₂;

Y is phenyl substituted with 0-2 R^{4a} or naphthyl substituted
with 0-2 R^{4a};

30

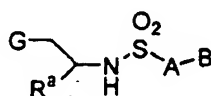
R⁴, at each occurrence, is selected from H, =O, OR², CH₂OR²,
F, Cl, Br, I, C₁₋₄ alkyl, NH₂, (CH₂)_rC(O)R^{2c}, and
C(O)NR²R^{2a};

R^{4a} , at each occurrence, is selected from H, OR^2 , CH_2OR^2 , F, Cl, Br, I, C_{1-4} alkyl, NH_2 , $(CH_2)_rC(O)R^{2c}$, and $C(O)NR^2R^{2a}$; and,

5 r , at each occurrence, is selected from 0, 1, and 2.

37. A compound according to Claim 3, wherein the compound is of the formula:

10



R^a is $C(O)$ -(6 membered heterocyclic system containing 1 N atom and substituted with 0-2 R^4);

15

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

20

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

25 alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

30

A is a 10 membered bicyclic heterocyclic system containing 1 N atom and substituted with 0-2 R^4 ;

B is H or Y;

Y is selected from:

C₃₋₆ carbocyclic residue substituted with 0-2 R^{4a}, and
5 5-6 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, OR², F, Cl,
10 Br, I, C₁₋₄ alkyl, NR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, and
CF₃;

R^{4a}, at each occurrence, is selected from H, =O, OR², F, Cl,
15 Br, I, C₁₋₄ alkyl, NR²R^{2a}, (CH₂)_rC(O)R^{2c}, C(O)NR²R^{2a}, and
CF₃;

r, at each occurrence, is selected from 0, 1, 2, and 3.

38. A compound according to Claim 37, wherein:

20 R^a is C(O)-(N-1,2,3,6-tetrahydropyridine substituted with
CO₂H);

alternatively R^a is C(O)-(N-1,2,3,6-tetrahydropyridine
25 substituted with CH₃);

A is 1,2,3,4-tetrahydroisoquinoline substituted with 1-2 R⁴;

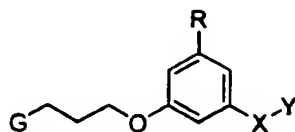
B is H;
30

R⁴, at each occurrence, is selected from H, methyl, =O, OR²,
F, Cl, Br, I, C₁₋₄ alkyl, NR²R^{2a}, (CH₂)_rC(O)R^{2c},
C(O)NR²R^{2a}, SO₂NR²R^{2a}, and CF₃;

35 r, at each occurrence, is selected from 0, 1, and 2.

39. A compound according to Claim 3, wherein the compound is of the formula:

5



R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

10

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c} , at each occurrence, is selected from OH, OCH_3 , OCH_2CH_3 , CH_3 , benzyl, and phenyl;

15

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

20

X is OSO_2 ;

25 Y is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^{4a} , and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a} ;

30

R^4 is H;

R^{4a} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3 ; and,

5 r , at each occurrence, is selected from 0, 1, 2, and 3.

40. A compound according to Claim 39, wherein:

10 R is methyl;

Y is selected from phenyl substituted with 0-2 R^{4a} , naphthyl substituted with 0-2 R^{4a} , and quinolinylyl substituted with 0-2 R^{4a} ;

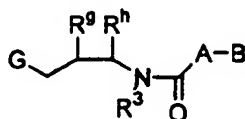
15

R^{4a} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and CF_3 ; and,

r , at each occurrence, is selected from 0, 1, and 2.

20

41. A compound according to Claim 3, wherein the compound is of the formula:



25

R^g is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

30 R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

R², at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

5 R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH₃, OCH₂CH₃, CH₃, benzyl, and phenyl;

10 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

15

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:

20 C₆₋₁₀ aromatic ring substituted with 0-2 R⁴, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

25 B is H or Y;

Y is selected from:

C₆₋₁₀ aromatic ring substituted with 0-2 R^{4a}, and 5-6 membered aromatic heterocyclic system containing
30 from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c},
35 C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

R^{4a} , at each occurrence, is selected from H, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, $-CN$, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;

5

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl, and benzyl;

10

p , at each occurrence, is selected from 0, 1, and 2; and,

r , at each occurrence, is selected from 0, 1, 2, and 3.

15

42. A compound according to Claim 41, wherein:

R^g is selected from CH_2OR^3 , and $CH_2C(O)OCH_3$;

20

R^h is selected from CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

A is phenyl;

B is Y;

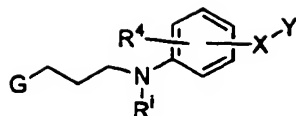
25 Y is phenyl substituted with 0-2 R^{4a} ;

R^{4a} , at each occurrence, is selected from H, OR^2 , Cl, Br, F, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $C(O)NR^2R^{2a}$, and CF_3 ; and,

30 r , at each occurrence, is selected from 0, 1, and 2.

43. A compound according to Claim 3, wherein the compound is of the formula:

35



R^1 is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and $C(O)OR^3$;

5

X is O;

Y is pyrrolidinyl substituted with 1-2 R^{4a} or piperidinyl substituted with 1-2 R^{4a} ;

10

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

15

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

20

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

25

R^4 , at each occurrence, is selected from H, F, Cl, Br, I, C_{1-4} alkyl, NR^2R^{2a} , and CF_3 ; and,

R^{4a} , at each occurrence, is selected from H, C_{1-4} alkyl, $CH_2NR^2R^{2a}$, and $C(=NR^2)CH_3$.

30

44. A compound according to Claim 43, wherein the compound is of the formula:

R^1 is selected from $SO_2CH_2C(O)OR^3$ and $C(O)CH_2C(O)OR^3$;

5

Y is piperidinyl substituted with 1-2 R^{4a} ;

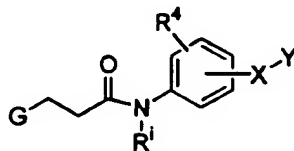
R^3 , at each occurrence, is selected from H and C_{1-4} alkyl;

10 R^4 is H; and,

R^{4a} , at each occurrence, is selected from H, C_{1-4} alkyl, $CH_2NR^2R^{2a}$, and $C(=NR^2)CH_3$.

15

45. A compound according to Claim 3, wherein the compound is of the formula:



R^1 is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and $C(O)OR^3$;

20

X is O;

Y is pyrrolidinyl substituted with 1-2 R^{4a} or piperidinyl substituted with 1-2 R^{4a} ;

25

R^2 , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

30 R^{2a} , at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

alternatively, R^2 and R^{2a} , together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^4 , at each occurrence, is selected from H, F, Cl, Br, I, C_{1-4} alkyl, NR^2R^{2a} , and CF_3 ; and,

R^{4a} , at each occurrence, is selected from H, C_{1-4} alkyl, $CH_2NR^2R^{2a}$, and $C(=NR^2)CH_3$.

46. A compound according to Claim 45, wherein the compound is of the formula:

R^i is selected from $SO_2CH_2C(O)OR^3$ and $C(O)CH_2C(O)OR^3$;

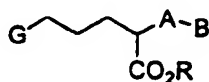
Y is piperidinyl substituted with 1-2 R^{4a} ;

R^3 , at each occurrence, is selected from H and C_{1-4} alkyl;

R^4 is H; and,

R^{4a} , at each occurrence, is selected from H, C_{1-4} alkyl, $CH_2NR^2R^{2a}$, and $C(=NR^2)CH_3$.

47. A compound according to Claim 3, wherein the compound is of the formula:



R is selected from H, C₁₋₄ alkyl, and NH₂;

5 R², at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

10 R^{2b}, at each occurrence, is selected from H, C₁₋₆ alkyl,
benzyl, and phenyl;

alternatively, R² and R^{2a}, together with the atom to which
they are attached, combine to form a 5 or 6 membered
15 saturated, partially saturated or unsaturated ring and
containing from 0-1 additional heteroatoms selected
from the group consisting of N, O, and S;

A is selected from:

20 C₆₋₁₀ aromatic ring substituted with 0-2 R⁴, and
5-10 membered aromatic heterocyclic system containing
from 1-4 heteroatoms selected from the group consisting of
N, O, and S substituted with 0-2 R⁴;

25 B is Y or X-Y;

X is O;

Y is selected from phenyl substituted with 0-2 R^{4a},
30 pyrrolidinyl substituted with 0-2 R^{4a}, and piperidinyl
substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, OH, CH₂OH, Cl,
Br, F, I, C₁₋₄ alkyl, -CN, (CH₂)_rNR²R^{2a}, C(O)NR²R^{2a}, and
35 CF₃;

R^{4a} , at each occurrence, is selected from H, OH, CH_2OH , Cl, Br, F, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, and CF_3 ;

5

n is 0 or 1; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

10

48. A compound according to Claim 47, wherein:

R is selected from H, methyl, ethyl, and NH_2 ;

15 A is phenyl substituted with 0-1 R^4 or thienyl substituted with 0-1 R^4 ;

B is Y or X-Y;

20 X is O;

Y is selected from phenyl substituted with 0-2 R^{4a} , pyrrolidinyl substituted with 0-2 R^{4a} , and piperidinyl substituted with 0-2 R^{4a} ;

25

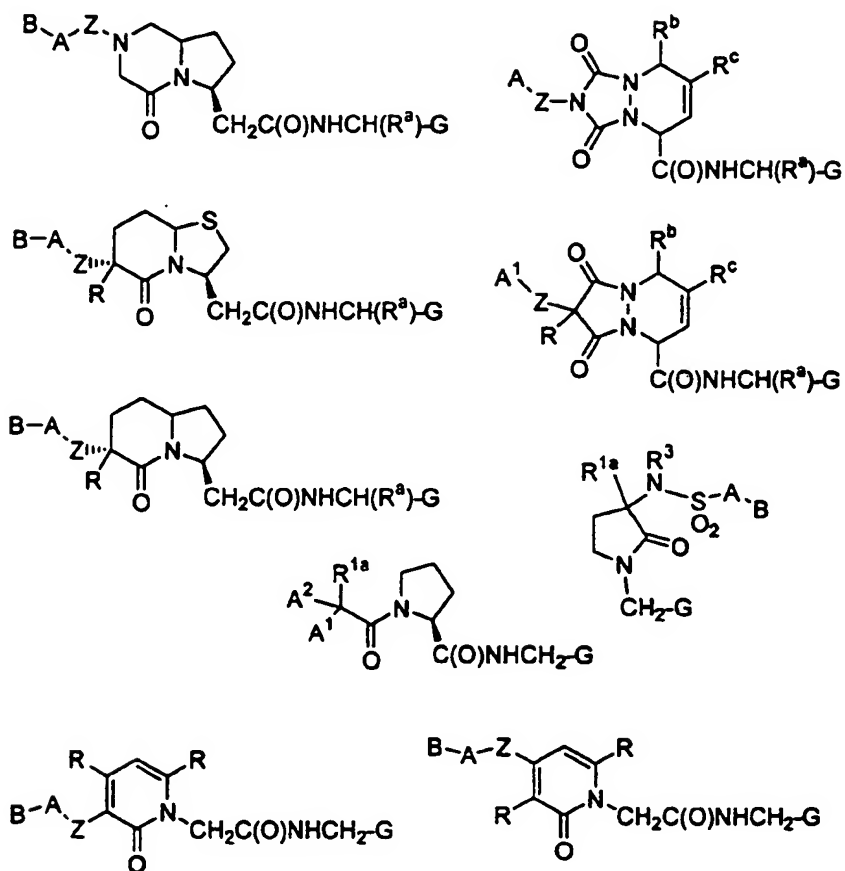
R^4 , at each occurrence, is selected from H, OH, CH_2OH , Cl, Br, F, I, C_{1-4} alkyl, NH_2 , $C(O)NH_2$, and CF_3 ;

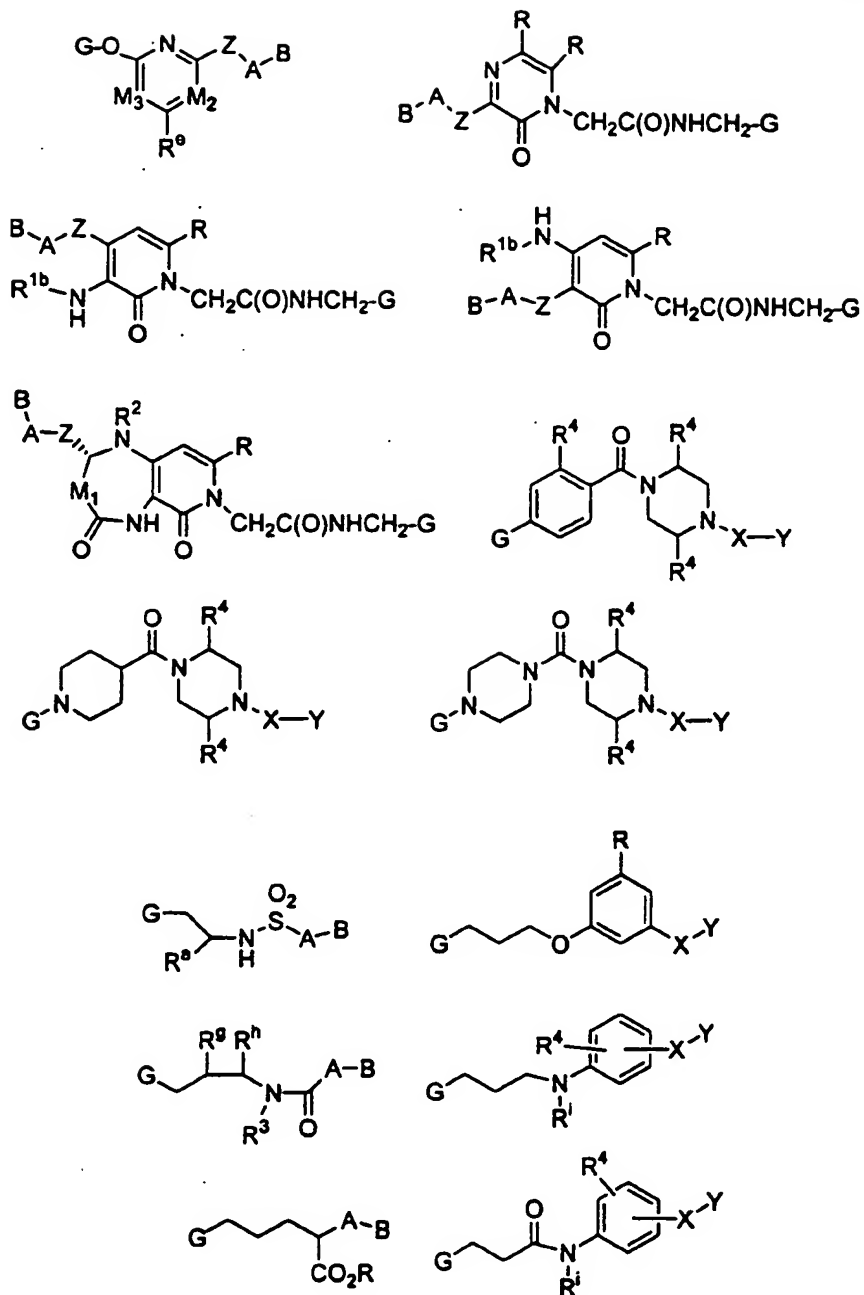
R^{4a} , at each occurrence, is selected from H, OH, CH_2OH , Cl,

30 Br, F, I, C_{1-4} alkyl, NH_2 , and $C(=NR^2)NR^2R^{2a}$; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

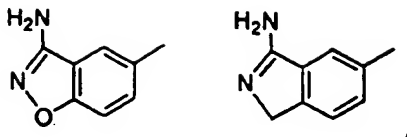
49. A compound according to Claim 3, wherein the compound is of the formula:





5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from:



R^a is selected from $C(O)C(O)OH$ and $C(O)$ (benzothiazol-2-yl);

5 R^g is selected from H, CH_2OR^3 , $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2 ;

R^h is selected from H, CH_2 -phenyl, CH_2CH_2 -phenyl, and $CH=CH$ -phenyl;

10

R^i is selected from $SO_2CH_2C(O)OH$ and $C(O)CH_2C(O)OH$, and $C(O)OR^3$;

15 R , at each occurrence, is selected from H, methyl, ethyl, benzyl, and NH_2 ;

R^2 , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl, and phenyl;

20 R^{2a} , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;

25

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

Z is $C(O)CH_2$ or $CONH$;

30

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4 ; and,

- B is selected from Y, X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};
- 5 R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;
- R^{4a} is selected from C₁₋₄ alkyl, CF₃, S(O)₂R⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;
- 10 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;
- X is CH₂ or C(O);
- 15 Y is selected from NR²R^{2a} and CH₂NR²R^{2a};
- p is selected from 0, 1, and 2; and,
- 20 r is selected from 0, 1, and 2.

50. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to one of Claims 1-49 or a pharmaceutically acceptable salt thereof.

25

51. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-49 or a pharmaceutically acceptable salt thereof.

30

35

52. Use of a compound according to one of Claims 1-49 in therapy.

- 5 53. Use of a compound according to one of Claims 1-49 for the manufacture of a medicament for the treatment of thrombosis or a disease mediated by factor Xa.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/30735

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 241/36; A61K 31/495

US CL : 544/349; 514/249

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/349; 514/249

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	PLUMMER, J.S. et al., Potent and Selective Bicyclic Lactam Inhibitors of Thrombin: Part 3 P1' Modifications, Bioorganic and Medicinal Chemistry Letters. March 1999, Vol. 9, No. 6, pages 835-840, especially page 837.	1-8, 10 and 49-53
A	WO 98/28326 A1 (BIOCHEM PHARMA INC.) 02 July 1998.	1-8, 10 and 49-53
A	WO 97/48706 A1 (WARNER-LAMBERT COMPANY) 24 December 1997.	1-8, 10 and 49-53

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" documents defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

documents of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A"

document member of the same patent family

Date of the actual completion of the international search

03 April 2000 (03.04.2000)

Date of mailing of the international search report

26 APR 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

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Authorized officer

Mukund Shah

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/30735

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8, 10 and 49-53

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/30735

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING: This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional fees must be paid.

Claims 1-53, drawn to compounds, compositions and method of use of 24 different base formulae and 20 different G moieties.

This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-CDLXXX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the various formulae on pages 136 and 137 differ significantly in chemical structure as well as the formulae of the G moieties.

Applicants are advised that they should pick one base formulae from claim 1 (pages 136-137) and one G group from claim 1 (pages 137-138).